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MODERN VIEWS ON THE TREATMENT AND PREVENTION OF HOOKWORM DISEASE *

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HOOKWORMS were first observed in man 104 years ago [1]; they were known to have become well-naturalized citizens of this hemisphere some 60 years later.[2] Although their etiological rôle was taken for granted prior to that time, most of our reasonably exact information concerning their life-history, transmission, distribution, social and economic significance and control has accumulated since the turn of the century. Many of these facts, familiar to parasitologists, have not yet found their way into medical texts. They appear intermittently in current medical journals in abbreviated form usually without interpretation. The object of this paper, therefore, is to present a synoptic review, momentarily up-to-date, of information about one of these items—namely, control—from the standpoint both of the private practitioner concerned with the cure of the sickness caused by hookworms and of the public health official whose basic aim is the prevention of hookworm disease.

Shortly after hookworms were recognized as being a cause of disease in man,[3, 4] their removal was attempted by means of drugs known to have anthelmintic values against other worms such as tapeworms and large roundworms. These included male-fern, cusso, kamala, santonin, turpentine, benzene, etc., but none of these was uniformly satisfactory, the best of the lot being the ethereal extract of male-fern.[4] This was rapidly replaced by thymol [5] which remained the standard anti-hookworm remedy for over 30 years, although beta-naphthol [6] was popular in some parts of the world, especially the Orient. In 1913, chenopodium, long known to have potent anthelmintic and some other less desirable properties, was reported on favorably [7] for its activity against hookworms and *Ascaris*. During the

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next decade, it was the drug of choice in expelling hookworms and is still used extensively for this purpose.

That brings us up to comparatively recent times. In 1921 a veterinary parasitologist, Maurice C. Hall,[8] working with compounds of carbon and chlorine, found that carbon tetrachloride was amazingly efficient in removing hookworms from dogs. Toxicity tests on dogs, monkeys and finally man seemed to justify its administration to cases of human hookworm disease and well over a million individuals have been treated with this drug.

It is undoubtedly the most effective and most conveniently administered hookworm anthelmintic now known. It is commonly employed in 3 or 4 c.c. doses for adults in water, milk or capsules either with or followed by saline purgation. It acts directly on the worms as it passes through the intestines, removing from 95 to 99 per cent of the type found in this country and completely defaunating from 60 to 90 per cent of the cases with a single treatment.

Carbon tetrachloride is not without its hazards, however. In the first place, it is occasionally, though rarely, toxic. The number of instances of severe poisoning and of death associated with its use is extremely small and might reasonably be charged to chance were it not for the fact that the majority of them manifest a uniformity of syndrome which is experimentally reproducible in lower animals by administration of the drug. This includes irritation of the gastrointestinal tract, excitability followed by depression, bilirubinemia, retention of guanidine in the blood, hypoglycemia and unconsciousness, sometimes with convulsions, not infrequently leading to death.

It has been clearly demonstrated that these effects are not generally due to overdoses of the drug nor to impurities contained in it. These unfortunate developments are difficult, if not impossible, to anticipate and occur without significant frequency in all groups except alcoholics. Lambert[9] treated 50,000 cases in Fiji without serious consequences and then had two deaths in a single week.

The chain of circumstances in these cases seems to be as follows: carbon tetrachloride, like its chemical sibling, chloroform, is an anesthetic with a strong predilection for hepatic tissues. The liver rapidly absorbs the drug from the blood and detoxicates it but, in some instances at least, is gravely injured by the process. This acute necrosis interferes with normal hepatic glycogenolysis and increases the amount of bile pigments in the blood. These combine with the blood calcium reducing the reserve calcium in the tissues and increasing its elimination from the body. The loss of ionized calcium in the blood may be one factor in the intoxication syndrome, but what seems to be of even greater importance is the abnormal accumulation of guanidine in the circulation. The elaboration of this noxious substance in unusual amounts is also due, presumably, to liver injury. Calcium has an antagonistic and highly beneficial effect in guanidine poisoning. The depletion of calcium, occasioned by the bilirubinemia permits high blood concentrations of guanidine with consequent toxic manifestations.

These demonstrations [10, 11] have led to important practices in the prevention or cure of carbon tetrachloride poisoning, namely the prophylactic or therapeutic use of diets rich in carbohydrates and calcium and poor in fats and meats and, under emergency conditions, the parenteral administration of calcium and sugar.

Two other circumstances may lead to complications in the use of this drug. The first of these is the consumption of alcohol either prior to or during treatment. The cirrhotic liver of chronic alcoholics is in no condition to withstand the unusual strain placed upon it by this preparation. Thus, it fails more rapidly and more frequently than does the normal liver, resulting in the succession of circumstances mentioned above. Alcohol taken *with* carbon tetrachloride frequently results in violent and continuous nausea and vomiting, sometimes with intestinal hemorrhage, jaundice, delirium, convulsions and death. Thus carbon tetrachloride should not be given to persons known to be habitually addicted to the use of alcohol and this stimulant should be strictly forbidden during treatment.

Heavy roundworm infections may also be a source of danger. This drug stimulates these large parasites to abnormal activity, resulting in the formation of solid plugs of their bodies obstructing the intestine or in their migration anteriorly into the common bile or pancreatic ducts or the pharynx whence they may be extruded through the mouth or nose. It is, therefore, of paramount importance (1) to ascertain by adequate laboratory examination whether or not ascarids as well as hookworms are present, and (2) if they are, to see to their removal before proceeding with carbon tetrachloride treatment. This may be readily accomplished with either chenopodium or hexylresorcinol.

In an effort to increase the antihookworm efficiency of carbon tetrachloride, to minimize its dangers when roundworms are present, and generally to facilitate anthelmintic treatment under such conditions, various mixtures of carbon tetrachloride and oil of chenopodium [9] or ascaridol,[12] its active principle, were introduced and have been very popular. These are highly effective combinations for the expulsion of both hookworms and roundworms but, it must be remembered, contain elements of danger from two sources rather than only one. These properties are not supplemental as the injuries caused by carbon tetrachloride are mainly hepatic, whereas those due to chenopodium are directed against the central nervous system. Such compound anthelmintics should be administered only under the careful supervision of a watchful physician.

Hall [13] likewise directed attention to the hookworm-removing attributes of tetrachlorethylene. It is closely related chemically to carbon tetrachloride and is used in the same dosage. Although it is not as effective as the other drug, it seems to be almost entirely devoid of its toxic propensities due to its lower solubility in aqueous systems and to its minimal absorption from the intestine. Its efficiency varies in the hands of different investigators. Our own observations on carefully controlled cases convince us that

although a single treatment will not get rid of the last hookworm from more than 50 per cent of our patients, it will remove about 90 per cent of all hookworms. Two treatments with tetrachlorethylene are about equivalent to and are much safer than a single dose of carbon tetrachloride in dislodging hookworms. In spite of its lower efficiency, it is preferred by most helminthologists because of its greater safety. There are virtually no contraindications to its use except alcoholism and ascariasis. A mixture of tetrachlorethylene and oil of chenopodium used under this last circumstance has received favorable report.[14]

The latest anthelmintic of significant merit is hexylresorcinol introduced as an ascaricide in 1930.[15] It is mentioned here because of its incidental hookworm-removal value. In 1 gm. doses for adults it removes practically all roundworms and about 70 per cent of the hookworms, though only a comparatively small percentage of patients are rendered hookworm-free from a single dose. If the pills are swallowed (not chewed), there are no known contraindications and it can be given repeatedly even to small children, aged persons and debilitated individuals. It is, therefore, an ideal drug for prehookworm treatment when *Ascaris* is present.

Briefly summarizing these current contributions to our knowledge of the treatment of hookworm disease, we may conclude that, from the standpoints of safety and efficiency, tetrachlorethylene is the best drug for use in uncomplicated hookworm infection. When roundworms are also present, hexylresorcinol followed by tetrachlorethylene or several hexylresorcinol treatments in rapid succession will give most satisfactory results. Carbon tetrachloride and oil of chenopodium are potent but unsafe anthelmintics; the older vermifuges lack both safety and efficiency.

In the public-health field of hookworm-disease prevention, similar shifts in principle and procedure have evolved. The activities of the Rockefeller Sanitary Commission from 1910 to 1914 had numerous and far-reaching effects. That their mass treatments served to reduce the incidence and, presumably, the intensity of hookworm infection in the southern states seems clearly indicated by the studies of Keller, Leathers and their associates.[16] The educational efforts which supplemented the treatment campaign generated interest in and a desire for local health facilities especially among rural populations. Perhaps the greatest consequence was the stimulation of scientific interest in the subject of hookworm disease and its control. Laboratory and field researches were carried on the world over.

Space and time limitations forbid the summarizing of the information gained as a result of these endeavors. It is interesting to note, however, that this study, like most intensive and extensive inquiries, progressed rapidly from the stage of qualitative exploration to that of quantitative analysis. This led to a concept of hookworm disease with which most medical men and many public health officials do not seem to be familiar.

Briefly expressed, it attempts to distinguish between *hookworm disease* in its most literal sense and *subclinical hookworm infection,* which is gen-

erally much more common. The distinction is based on the number of worms present and the nutritional status of the host as shown in the following argument with its implications concerning hookworm-disease control.

1. Adult hookworms suck blood continuously. The amount removed is *proportional to the number of hookworms present.*
2. If they remove blood more rapidly than it can be formed *HOOKWORM DISEASE* (*anemia*) *results; if not,* the condition is one of *subclinical hookworm infection.*
3. The primary objective of public health authorities should be the *detection, prevention and control of HOOKWORM DISEASE* rather than the elimination of subclinical hookworm infection.
4. Inasmuch as the rate of blood removal by hookworms varies directly with the number present and the rate of hemoglobin formation is normally governed by iron and protein intake, it follows that
    a. Hookworm disease is more likely to occur and will be more severe when worm burdens are high and iron-protein consumption low.
    b. When adequate iron-protein consumption prevails, hookworm infection, with rare exceptions, will be subclinical whether worm burdens are heavy or light.
    c. When diets are iron-protein deficient, a chronic, progressive anemia will develop irrespective of the presence or absence of hookworms.
5. Therefore, even in hookworm-infested areas, all instances of anemia are not necessarily cases of hookworm disease. *Intelligently planned hookworm-disease control must distinguish between anemias caused or augmented by hookworms and those due to other causes.*
6. To accomplish the control of hookworm disease, knowledge of the *intensity* as well as the *incidence* of hookworm infection must be considered in relation to the *non-hookworm anemias* of the people concerned.

In considering this reasoning, it must be remembered that hookworm, like many other helminthic infections, is fundamentally different from bacterial or protozoan infections in that the causative organism—hookworms—does *not* multiply within the body of its host. Indeed, there is good evidence to show [17] that if the entrance of hookworm larvae to the body is prevented, the number of hookworms remaining not only fails to increase but actually diminishes at a relatively rapid rate. This, of course, is the basis for public health reliance upon sanitary excreta-disposal facilities for homes and schools in the control of hookworm disease.

Thus, emphasis is shifting from hookworm infection to hookworm disease. We no longer advocate the random examination of school children, but rather the selective survey of anemic persons in school or out, under 20

years of age. This amounts to an investigation of "suspects." Stool specimens are examined in the laboratory first of all by brine flotation to identify all egg-positive individuals. Their stools are then subjected to an egg-counting procedure which indicates the approximate number of hookworm eggs per unit of stool. Inasmuch as the number of worms present varies directly with the magnitude of the egg-count, this gives a rough measure of the intensity of the infection, permitting the separation of persons with a sufficiently heavy worm-burden to cause anemia from those whose worm burdens are so light that the observed anemia is probably due to some

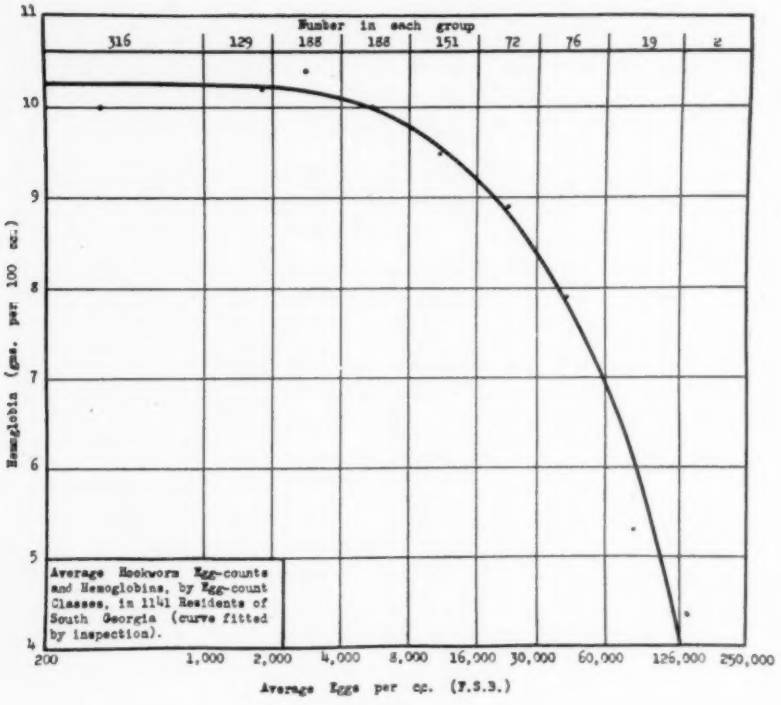

FIG. 1.

cause other than hookworms. Here in Georgia we have set 5,000 eggs per c.c., an egg-concentration which is roughly equivalent to 200 worms, as the level above which we will do hookworm-control follow-up, below which we ignore the presence of hookworms and start looking for some other cause of anemia. Our basis for this particular figure is shown in the accompanying curve (figure 1) in which it is apparent that not much change in hemoglobin levels is associated with hookworm infection until worm burdens equivalent to 5,000 eggs per c.c. are reached.

Modern hookworm investigation-and-control technic centers on the family instead of the individual. The probability of high rates of family incidence is obvious when one considers that the infection is transmitted

primarily through bare feet in contact with polluted soil. This combination of circumstances occurs most frequently in the environs of the home and is more likely to occur around certain homes than around others. Thus, the

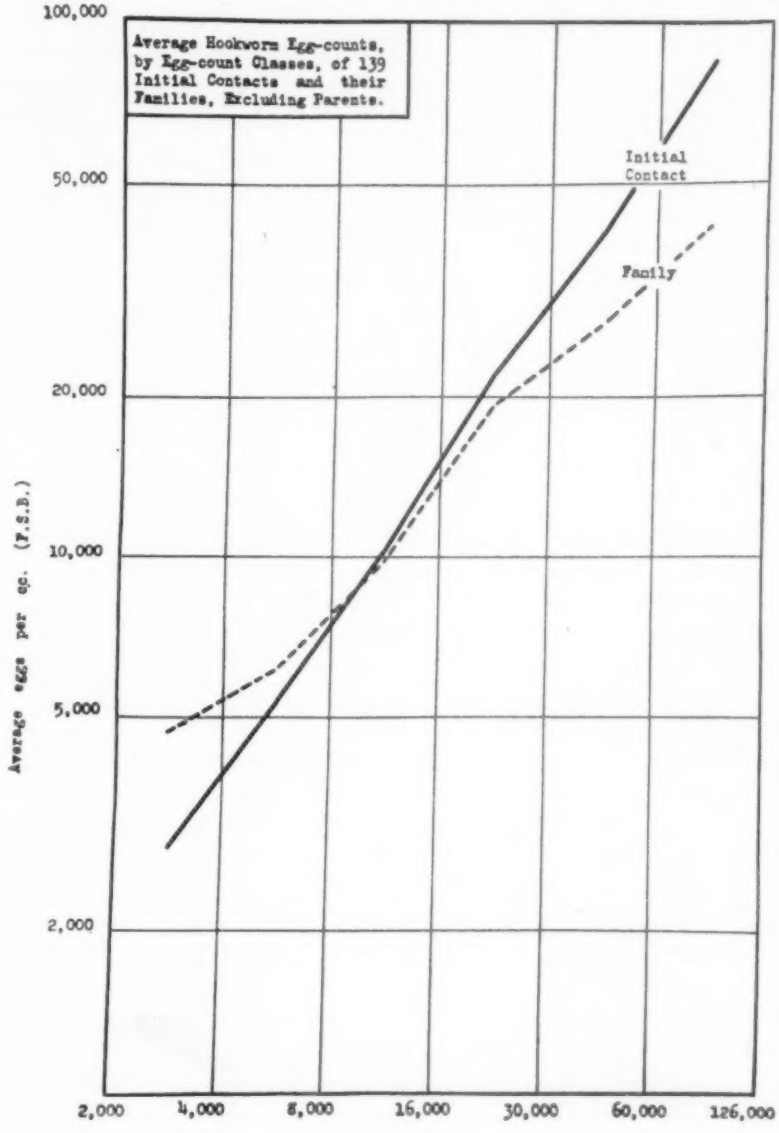

FIG. 2.

intensity as well as the incidence of infection revolves around the family. This is indicated in the accompanying figure (figure 2) in which the solid line represents the locus of average egg-counts, by egg-count classes, of "initial contacts," that is, the first anemic member of the family seen, under

20 years of age, while the broken line shows the same information for the 139 families of which they are members. It will be observed that the average egg-counts of the families increase with those of the "initial contacts"; thus, the intensity of infection in the initial contact turns out to be fairly representative of the average family worm burden. This means that families needing hookworm relief can be identified from these initial contacts and that, as a general rule, it is unnecessary to examine other members of the suspected families if, for example, group treatment is planned as the control measure.

What is to be done for these hookworm-disease families once they are identified? First of all, their sick members must be made well. This requires medical service, and as far as possible, is handled by private physicians in Georgia. Indigency is high, however, among hookworm sufferers, and it is usually the expressed desire of local medical groups or practitioners that health doctors assume treatment responsibilities for such patients. Anthelminthic drugs are supplied gratis to medical men by the State.

The therapeutic problem is a dual one consisting of worm removal and treatment of the anemia. As Payne and Payne [19] and others [18, 20] have recently shown, hemoglobin recovery following worm expulsion without iron therapy is a long-drawn-out process. This is especially true when dietaries are iron deficient. On the other hand although iron administration alone produces rapid improvement in the blood picture, the gains are not sustained unless the worms are removed.[19, 20] In Georgia we do both, giving iron, usually as Blaud's pills, *before* deworming if the anemia is exceptionally severe, i.e., hemoglobin level of 5 gm. or less; *after* worm removal if the anemia is moderate. Educational efforts are made thereafter, to improve the dietary so that greater iron intake in food is provided especially for growing children in whom the concurrence of hookworm anemia and nutritional anemia is most marked.

The prevention of hookworm disease is, first of all, a matter of sanitation, i.e., the provision of approved excreta-disposal facilities; secondly, education concerning their use and the physical benefits that will result therefrom. The sale and use of sanitary sewage-disposal structures for homes and schools is, therefore, vigorously promoted but in these days of progressively restricted WPA participation in community sanitation projects, of increasing costs and decreasing availability of materials and of labor, the prospects of preventing any great amount of hookworm transmission by the use of standard sanitary units are comparatively remote. Families that cannot afford minimal medical service cannot afford pit privies.

In those numerous instances, therefore, in which home sanitation cannot be provided, an attempt is being made in this State to develop more definitely preventive values from anthelmintic treatment than it provides as ordinarily administered.

As indicated above, individuals suffering from hookworm anemia are treated with iron and tetrachlorethylene as fast as they are discovered ir-

respective of whether or not the premises are to be sanitated. The deworming of other members of the family at that time is not encouraged. If a pit privy is provided and used, there will be no increase in the intensity of infection and so family treatment is not necessary. If, however, the household must get along without sanitary facilities, at least one and desirably two worm-removal treatments are urged for *all* members of the family during the cold winter months of the year. The object here is to reduce and, if possible, to eliminate the family worm burden at a time when immediate reinfection is less likely than during the summer months. The unfavorable effect on non-parasitic stages of hookworms of temperatures below 50° F. has been noted by various observers. Augustine,[21] working in southern Alabama, was unable to find larvae in polluted soil from the latter part of December into March. Our own findings in south Georgia, incomplete and inconclusive, confirm this observation. Thus it appears that the soil in this area tends to become free from infective larvae during the winter months and the likelihood of reinfection following treatment at this season is correspondingly remote. This seasonal prophylactic effect is enhanced by the fact that it is during the cold months of the year that rural residents wear shoes if they ever wear them at all.

A last anti-hookworm possibility, at present in its incipient stage, may in the long run surpass in importance either sanitation or treatment. The experiments of Cort and Otto [22] and their students [23, 24, 25] on hookworm disease in dogs suggest (1) that a highly protective, specific immunity to hookworms and hookworm disease may be developed by experience with the infection, and (2) that this resistance can be broken and rendered ineffective by dietary deficiency. This effect is entirely separate and distinct from the inability to exert hematopoietic potentialities to their utmost because of inadequate iron-and-protein consumption. Its most striking demonstration is in the case of previously immunized dogs whose resistance, reduced by deficient diet, is suddenly restored by adequate dietary supplements. Under these conditions, the dogs recover clinically, lose worms spontaneously and resist further infection.

It would be entirely premature to assume from the above that the man-hookworm system will interact as the dog-hookworm system has been shown to do. Nevertheless, there is abundant epidemiologic evidence to suggest that this relationship may prevail and, as far as I know, none to refute it. Perhaps the time may come, therefore, when we will know that we can prevent and cure human hookworm disease by dietary manipulation, income and gustatory fancy permitting.

In summarizing the preventive aspects of this subject, it may be said that although sanitation, treatment and education remain the familiar armamentarium of the hookworm fighter, their application is now ordered and refined as never before (1) by discrimination between hookworm disease and subclinical hookworm infection, (2) by differentiating between the anemia due to hookworms and those due to other causes, and (3) by the

recognition of the family rather than the individual as the unit of investigation and control. The relation of diet to hookworm infection and its prevention is already known to be important; present knowledge suggests that it may become more so in the future.

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MYELOID HYPERPLASIA AND METAPLASIA INDUCED BY EXTRACTS OF URINE FROM PATIENTS WITH MYELOGENOUS LEUKEMIA *

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In previous brief reports,[1, 2] the effect in guinea pigs of injection of extracts of urine from patients with leukemia has been described. The results indicated that extracts of urine from patients with chronic myeloid leukemia produced myeloid hyperplasia and metaplasia in the organs of guinea pigs with considerably greater frequency than did extracts of urine from patients with other diseases and from normal people.

Four different methods of extraction were effective in recovering the active material from the urine of patients with chronic myeloid leukemia. These included the original kaolin adsorption, a benzoic acid adsorption, and a chloroform extraction. The product of the latter was divided into two fractions, both of which had some activity. All of these methods have been adapted from standard procedures used to recover certain of the endocrine products from urine.

Experimental

Urine was obtained from patients with chronic myeloid leukemia, acute myeloid leukemia, chronic lymphoid leukemia, acute lymphoid leukemia, acute monocytic leukemia (Schilling type), Hodgkin's disease, multiple myeloma, aplastic anemia, infectious mononucleosis, and carcinomatosis. Sufficient urine could not be obtained from each type of disease to make extracts by each of the methods, and the major part of the investigation was done with extracts of urine from patients with chronic myeloid leukemia, chronic lymphoid leukemia, and from normal individuals.

Guinea pigs were employed as experimental animals. These were young, male animals weighing between 180 and 250 grams at the beginning of the experiment. No attempt was made to secure a uniform strain. The guinea pig was selected because it is a convenient size and because spontaneous leukemia seldom occurs in this animal. Mice, rats, rabbits, and monkeys were used in small numbers but because of difficulties encountered, further experimentation with them has been postponed.

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† Williams Memorial Fellow in Medicine, financed by a grant from the Edward Mason Williams Fund.

Guinea pigs received the extracts of urine in daily subcutaneous injections varying in volume from 0.1 to 10 c.c. and representing from 60 c.c. to 800 c.c. of original urine. Details of dosage will be amplified as each extract is described. The injections were continued for a period generally not exceeding 10 weeks, if death had not occurred sooner. Most of the animals died or were sacrificed within that period of time.

Complete autopsy was performed as soon after death as possible. The wet weight of the spleen and liver were recorded routinely. Sections were obtained from femoral, tibial, and humeral marrows, spleen, liver, lymph nodes, kidney, adrenal, heart, and lungs. Imprint films were made of marrow, spleen, and liver and stained with Wright's stain. Slices of the organs were placed in acid-Zenker's solution, and the sections made from these were stained with hematoxylin and eosin. Special stains on fixed tissue sections, including Wright, Mallory, Maximow, and Giemsa stains were made in several instances. The peripheral blood of the animals was examined not less than once a week during the course of the injections. This examination included a hemoglobin estimation (Sahli method), white blood count, and differential blood count.

Results

Approximately half the animals receiving extracts of urine from patients with chronic myeloid leukemia showed evidence of myeloid hyperplasia and metaplasia. Only about 15 per cent of animals receiving extracts of urine from individuals not having myeloid leukemia showed a similar response, and in these animals, the response was generally less marked.

Many of the animals which subsequently showed the myeloid response became ill, and either failed to gain or actually lost weight. The changes in the blood of these animals were not constant. In a great many animals, nothing more than a mild anemia was noted. In some, a severe hypochromic anemia, with hemoglobin as low as 45 per cent (7.0 grams) developed. Nucleated red cells and polychromatophilia were present. A few of these animals had free blood in the peritoneal cavity at autopsy, the exact origin of which could not be determined.

The white blood counts ranged from normal to moderately elevated, few being in excess of 25,000. The majority of cells were adult polymorphonuclear neutrophiles. In animals with elevated white blood counts, a small number of myelocytes and blast cells were present. The blood platelets were not altered. We do not feel that the changes in the peripheral blood were specific. They probably only reflected the general condition of the animal.

There was little gross change in the organs at autopsy. In some animals, the spleen was considerably enlarged, weighing as much as 4.0 grams. Some of the smallest spleens (0.25 gram wet weight), however,

showed the most marked histological changes. On cutting the spleens, the follicular structure was found to be obliterated or less prominent than normal. The bone marrow generally appeared grossly normal, although in a few instances it was redder and less fatty than normal. Other organs did not show any gross changes.

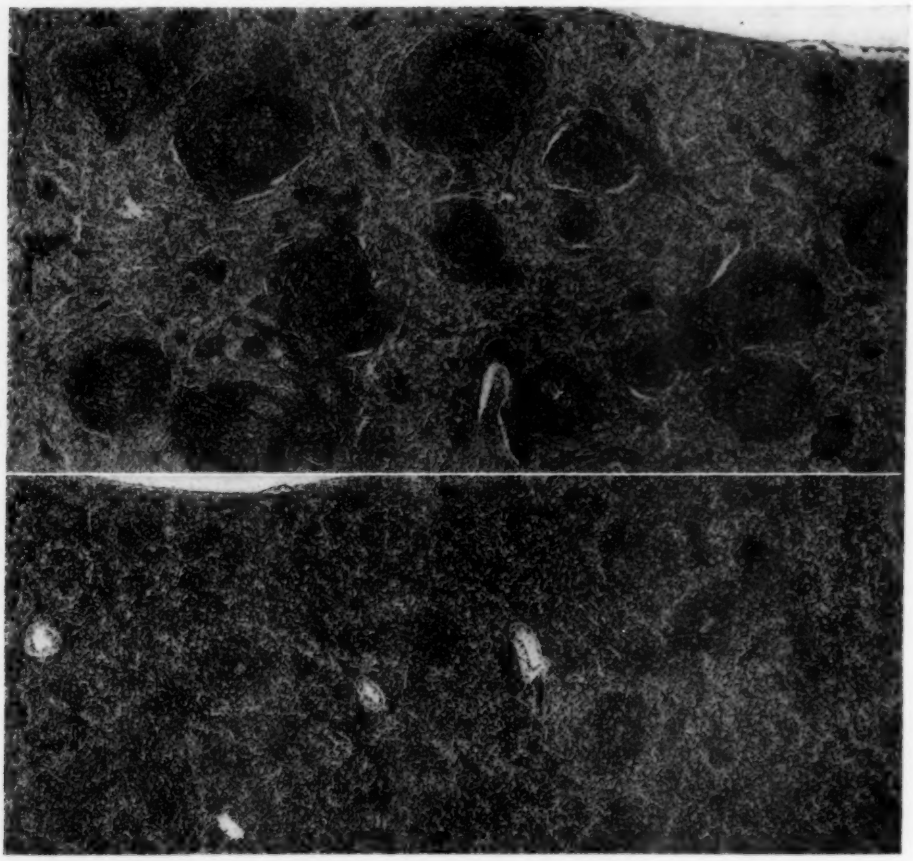

FIG. 1. Comparison of spleen from guinea pig given extract of urine from normal individual (above) with spleen from guinea pig given extract of urine from patient with chronic myeloid leukemia (below). Low power, 27 ×.

Histological changes, in contrast, were marked, and supplied the criteria for judging the degree of myeloid change present.

Figure 1 is a low power comparison of the spleen of an animal showing the myeloid change with that of an animal not showing such a change. The loss of prominence of follicular structure is at once apparent. Figure 2 is a higher power view to show the general nature of the cellular response in the spleen. The myeloid change is produced by the presence of cells, including blasts, myelocytes, and adult polymorphonuclear neutrophiles.

Cells undergoing mitotic division are present, as are also multinuclear giant cells, histologically identical with megakaryocytes.

The bone marrow of animals showing the myeloid reaction contained an increased number of immature granulocytes. In many instances there were also present increased numbers of immature red cells. There was a

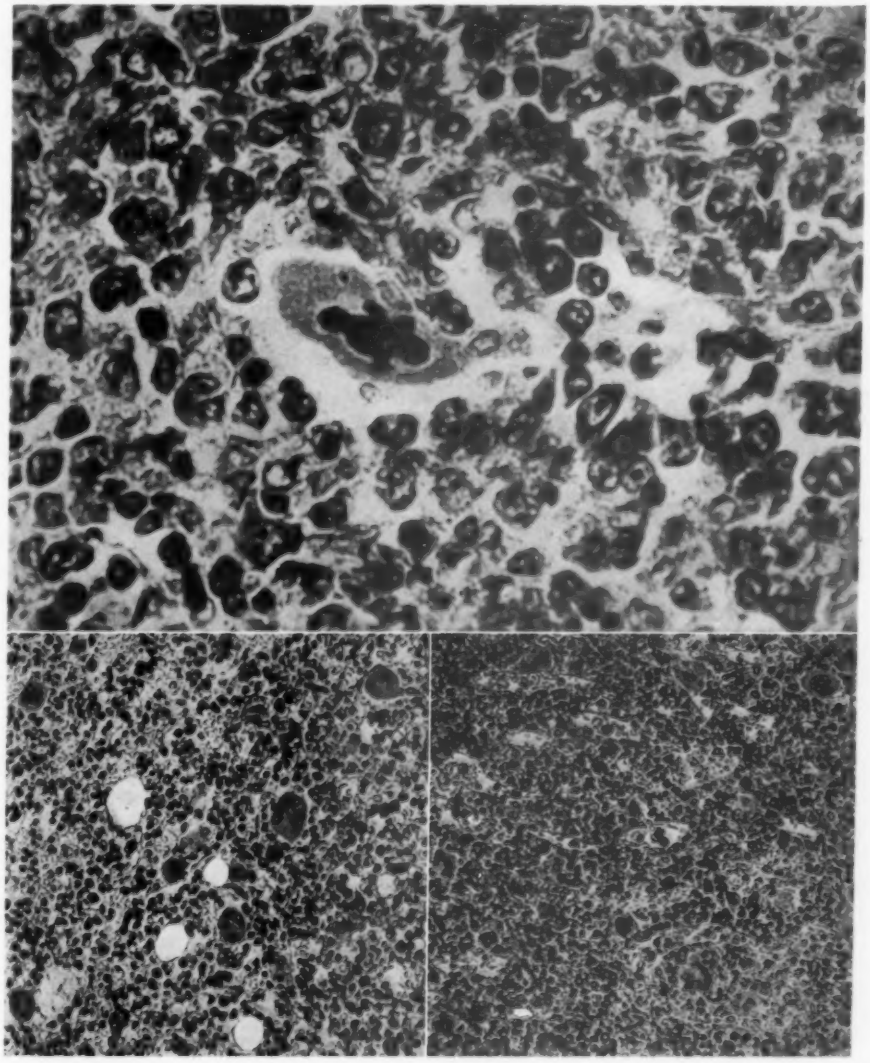

FIG. 2 (above). Spleen from guinea pig given extract of urine from patient with chronic myeloid leukemia showing presence of immature myeloid cells and megakaryocyte. High power, 590 ×.

FIG. 3 (below). Tibial bone marrow from guinea pig given extract of urine from normal individual (left) and from guinea pig given extract of urine from patient with chronic myeloid leukemia (right) to show decreased amount of fat and increased cellularity. Low power, 158 ×.

compensatory reduction of fat. Figure 3 is a low power comparison of the femoral marrow of an animal receiving extract of urine from a normal individual. Figure 4 shows high power views of unfixed marrow imprints.

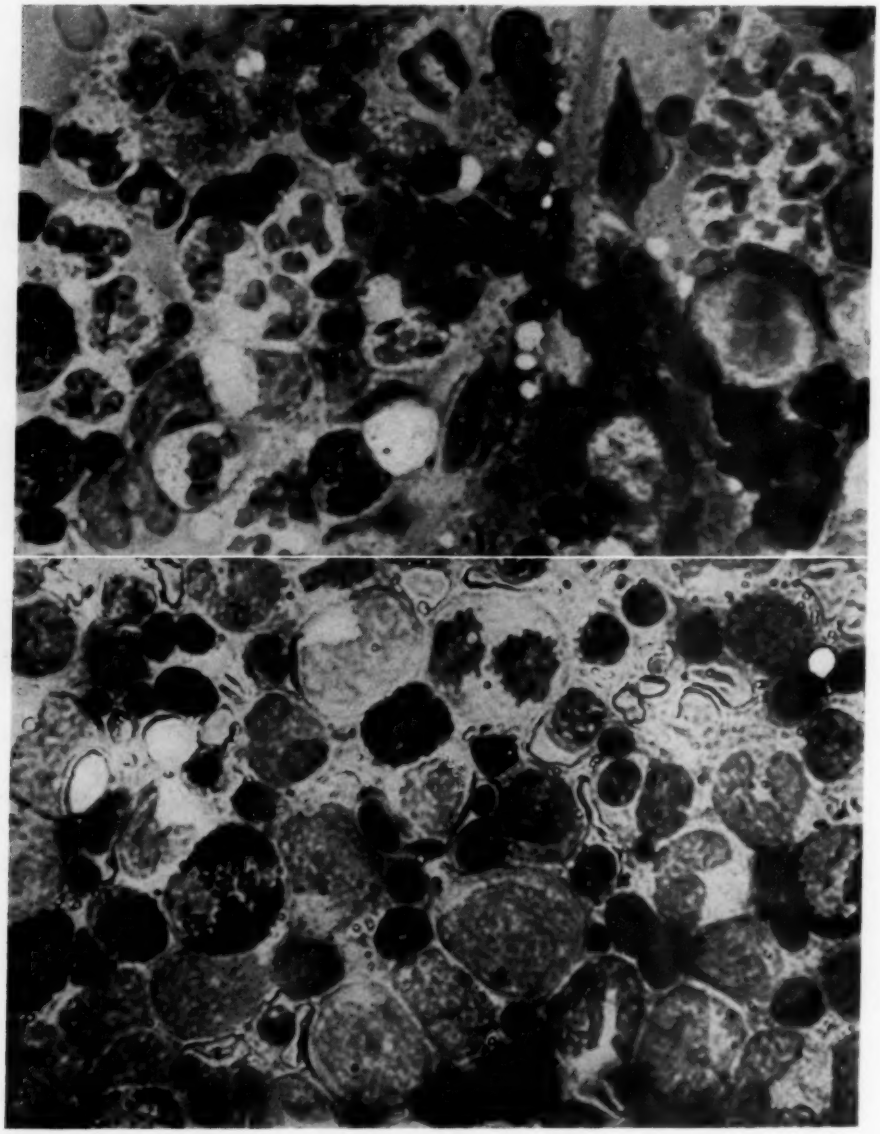

FIG. 4. Bone marrow imprints, Wright's stain. From guinea pig given extract of urine from normal individual (above) and from guinea pig given extract of urine from patient with chronic myeloid leukemia (below). High power, 800 ×.

These changes in the spleen and bone marrow were the most constant, and no animal was considered to show the myeloid response unless they were

present to some degree. Other organs frequently showed myeloid metaplasia, however.

Figure 5 shows the liver of an animal showing myeloid metaplasia. The abnormal cells were typically found in perivascular and periportal sites and

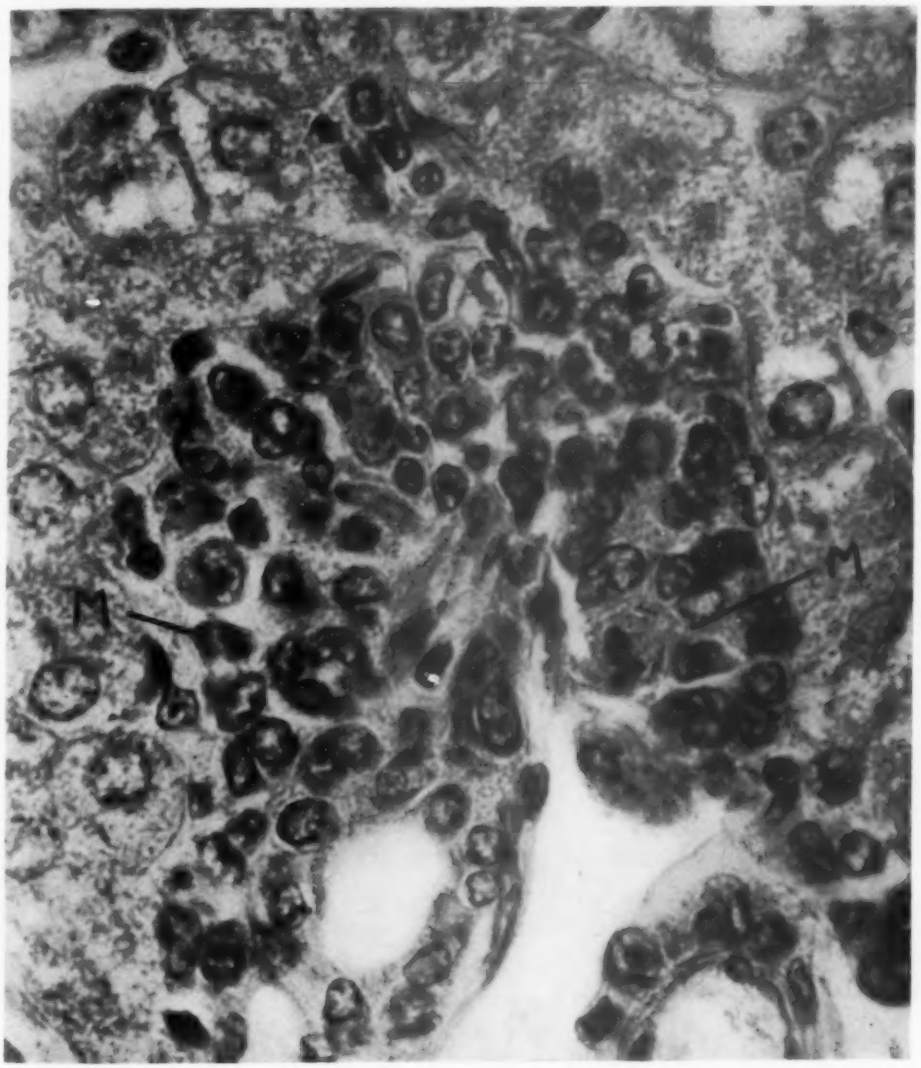

FIG. 5. Section of liver from guinea pig given extract of urine from patient with chronic myeloid leukemia showing myeloid infiltration in periportal area. Two cells in mitosis (M) are visible. High power, 1000 ×.

consisted of mature and immature granulocytes, including blast cells and cells undergoing mitotic division.

Myeloid metaplasia frequently occurred in the suprarenal gland where

it was found in the cortex, immediately beneath the capsule, and between the cords of cortical cells. Figure 6 shows an area of adrenal cortex containing mature and immature granulocytes.

Another observation of interest was that the lungs of guinea pigs receiving extracts of urine from normal people or patients with chronic lymphoid leukemia, showed a considerable amount of lymphoid activity

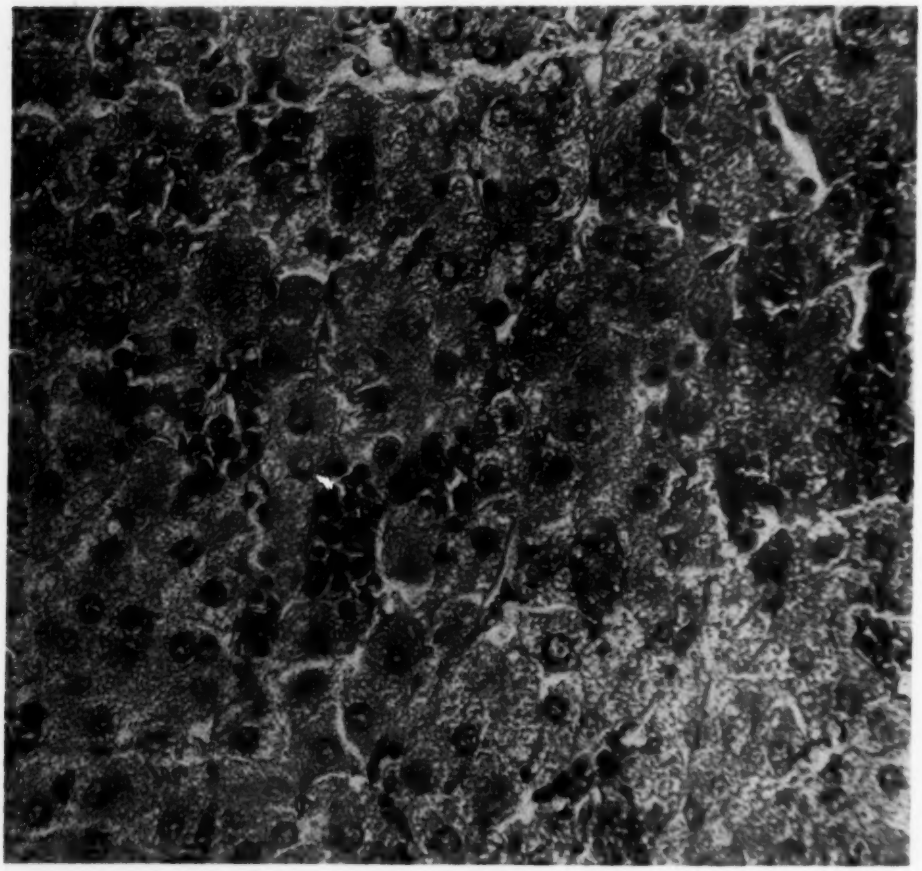

FIG. 6. Section of suprarenal cortex from guinea pig given extract of urine from patient with chronic myeloid leukemia showing infiltration with myeloid cells. High power, 590 ×.

around small, peripheral blood vessels. In such animals there was a cuff of mature and immature lymphocytes around nearly every vessel. This is shown in figure 7. In animals showing the myeloid response, such lymphoid activity was absent or greatly diminished. This is shown in figure 8. A similar state of affairs existed in the kidneys. Guinea pigs receiving extract of urine from normal individuals or patients with chronic lymphoid leukemia had kidneys which contained a variable number of small mononuclear cells,

presumably lymphocytes, in the spaces between the glomeruli and proximal convoluted tubules. Kidneys from guinea pigs showing the myeloid response did not contain such cells.

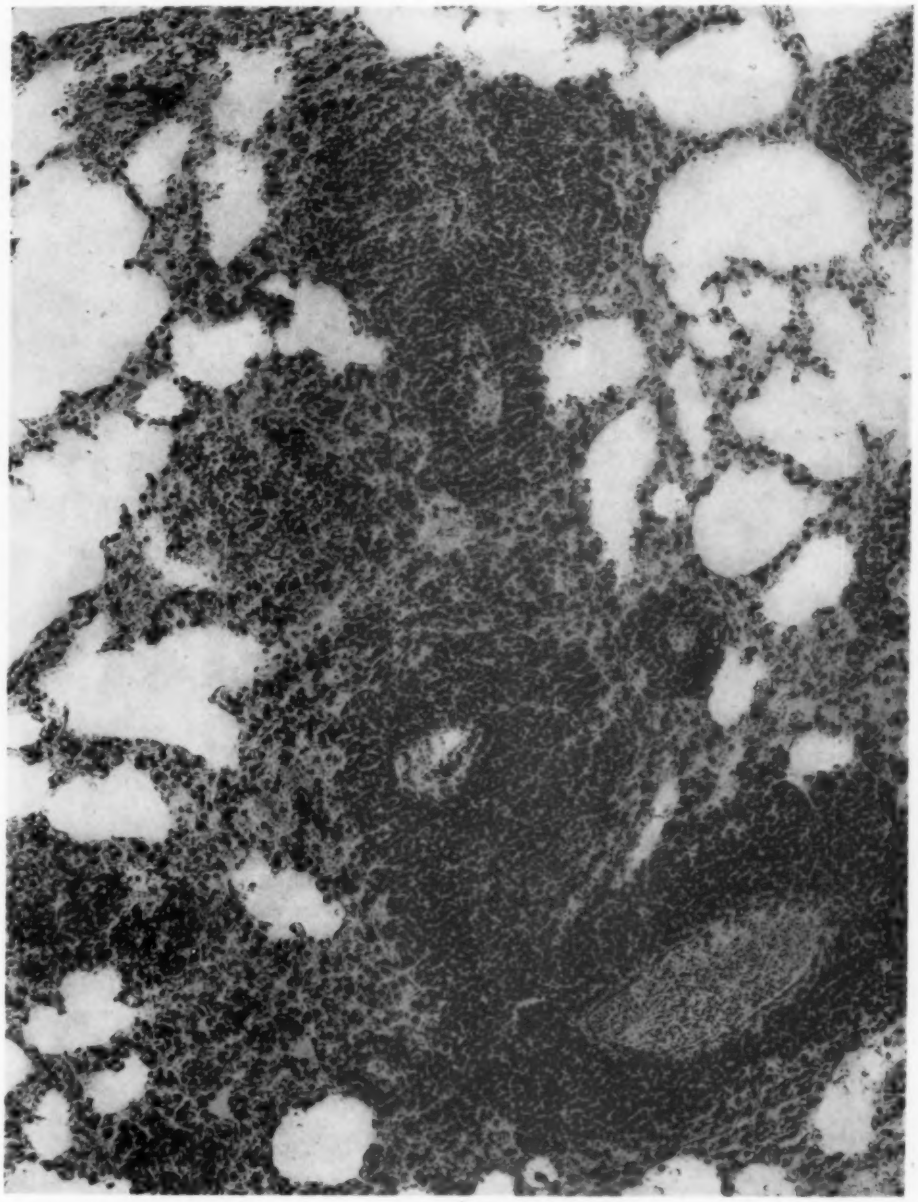

FIG. 7. Section of lung from guinea pig given extract of urine from patient with chronic lymphoid leukemia showing large numbers of mature and immature lymphocytes surrounding blood vessels at periphery of lung. Extract of urine from normal individuals produces a similar picture. Low power, 135 ×.

The lymph nodes did not participate in the myeloid metaplasia. Guinea pigs showing myeloid hyperplasia and metaplasia generally had normal appearing, inactive nodes, as compared with the more active lymphoid tissue of other guinea pigs.

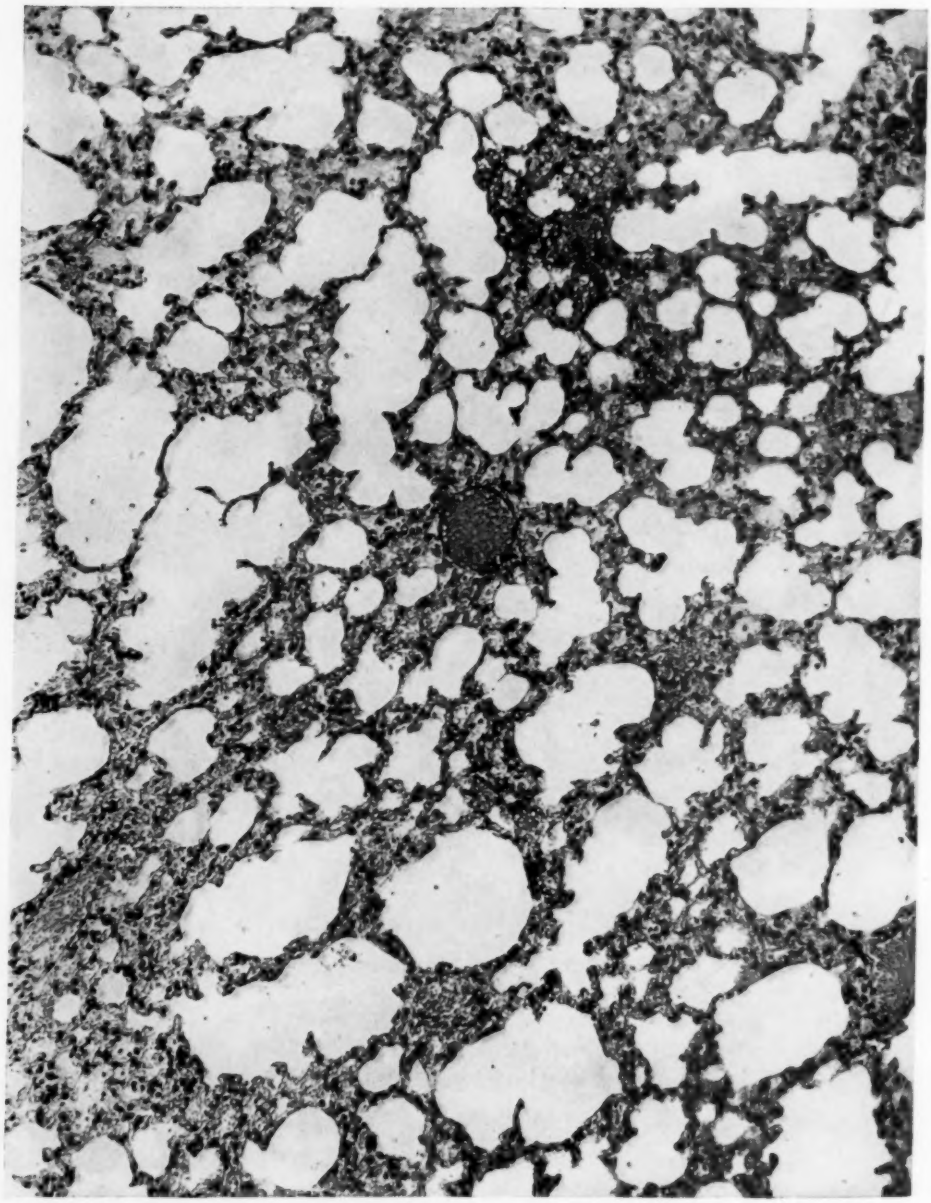

FIG. 8. Section of lung from guinea pig given extract of urine from patient with chronic myeloid leukemia to demonstrate absence of lymphoid activity. Compare with figure 7. Low power, 135 ×.

For purposes of classification in discussing the various extracts, the myeloid reaction just described has been graded as +++, ++, +, and ±, depending upon the degree of change present. A +++ response indicates changes in all of the organs as described above whereas a ± response indicates changes only in the spleen and marrow and such changes, although qualitatively identical with those described, are quantitatively less.

The classification of "erythroblastic" is included in the charts. Animals in this group showed large numbers of nucleated red cells in the organs of the hematopoietic system. When the reaction was less marked, the normoblast was the predominant cell. When the reaction was greater, large numbers of true blast cells (presumably megaloblasts) were found in association with the more mature normoblasts. Such cells were present in spleen, liver, marrow and suprarenal glands. There was no disturbance of the granulocyte series in these animals, the reaction apparently being limited to the erythrocyte series. The significance of the reaction is not entirely clear but we believe it represents a non-specific stimulation which occurs because of a peculiar susceptibility in certain of the guinea pigs.

Animals not having any of the characteristics listed above were classified as negative.

Results with Kaolin Extract. Method: This method was adapted from that described by Houssay and Biasotti.[3] Urine was obtained from patients with chronic myeloid leukemia, chronic lymphoid leukemia, Hodgkin's disease, acute monocytic leukemia, multiple myeloma, infectious mononucleosis, carcinomatosis, and from normal individuals. Eight to 10 liters were extracted at one time. Enough concentrated HCl was added to make the pH approximately 1.5 using thymol blue as an indicator. The acidified urine was placed in a five gallon carboy and 10 grams of colloidal kaolin (Merck) were added per liter of urine. The carboy was agitated vigorously once or twice an hour for about eight hours. It was then placed in a cold room (40 to 50° F.) overnight to allow the kaolin to settle. The supernatant urine was removed by siphon and about one liter of water added and mixed with the kaolin. This mixture was filtered on a Buchner funnel with suction until the kaolin was only damp. Sixty-six per cent alcohol, 100 c.c. per original liter of urine, was then added to the kaolin and was mixed thoroughly four or five times during the next two hours. The alcohol was separated from the kaolin on a Buchner funnel with suction and the kaolin discarded. The clear, brown, alcoholic solution was placed in an evaporating dish and the alcohol evaporated in a fan blast at room temperature. After the alcohol had evaporated, an acid insoluble precipitate formed. Enough 10 per cent sodium hydroxide was added to adjust the pH to 7.5 to 8.0 using brom-thymol blue as an indicator. The addition of the alkali dissolved the precipitate completely. Distilled water was added so that 1 c.c. of the extract represented 33 c.c. of original urine. The extract was passed through a Berkefeld V filter and stored in sterile bottles.

This material was injected subcutaneously into guinea pigs in doses of 4 to 10 c.c. daily, most animals receiving two doses of 4 c.c. daily. Many of the animals receiving this extract of urine made from patients with chronic myeloid leukemia died between the fifth and eighth week of injection. If death had not occurred by the tenth week, the animals were generally sacrificed. A few were maintained for longer periods. Animals receiving extracts of urine from patients not having chronic myeloid leukemia generally remained well.

The results obtained with this extract are shown in table 1. The myeloid leukemia urine extract produced myeloid change with greater frequency than did the other types of urine extracts, 13 of 26 animals showing such myeloid reaction. Two of 15 animals receiving normal urine extract showed a + myeloid response and two animals receiving urine extract from a patient with multiple myeloma showed weakly positive myeloid reactions. One animal

TABLE I

Results Obtained with the Kaolin Extract

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Hodgkin's Disease	Acute Monocytic Leukemia	Multiple Myeloma	Miscellaneous
Myeloid reaction							
+++	8						
++	4						2
+	1		2			1	
±						1	
Erythroblastic	1	1					
Negative	12	5	13	2	2		3

receiving urine extract from a patient with infectious mononucleosis and another animal receiving urine from a patient with aplastic anemia showed strong positive myeloid reactions. These two animals are included under miscellaneous in table 1. Three other animals receiving urine extracts from patients with polycythemia rubra vera and carcinomatosis did not show positive myeloid reactions. Two of the 15 guinea pigs receiving urine extract from normal individuals showed a positive myeloid response. None of the six animals receiving extract of urine from chronic lymphoid leukemia patients had a positive myeloid reaction.

Benzoic Acid Extract. Method: This method was adapted from that described by Katzman and Doisy.[4] Urine was collected from patients with chronic myeloid leukemia, chronic lymphoid leukemia, acute monocytic leukemia, and from normal individuals and preserved with chloroform (10 to 20 c.c. per liter). Glacial acetic acid was added in sufficient quantity to reduce the pH to 4–5 using methyl red-methylene blue as an indicator. The acidified urine was filtered through coarse paper and the precipitate discarded. A saturated solution of benzoic acid in acetone was added to the filtered urine in amounts of 50 c.c. per liter, with vigorous stirring. The benzoic acid pre-

cipitated immediately, and after a short time allowed for settling was separated by filtration on a Buchner funnel. To the benzoic acid was added a volume of acetone equal in volume to that in which the benzoic acid was originally dissolved. The acetone insoluble material was allowed to settle out and most of the supernatant material was siphoned off. The remainder, including the precipitate, was separated by centrifuging. The precipitate was washed five times with acetone to remove the remaining benzoic acid. The precipitate was next washed three times with distilled water (using 25 c.c. of water for each liter of urine unless larger amounts of urine were handled at one time. In the latter event, we used 300 to 500 c.c. distilled water per 100 liters of urine.) This preparation yields the material soluble in an acid medium and was found to have little or no activity when administered to animals. The precipitate was resuspended in a small amount of water and the pH adjusted to 7.5–7.8 by the addition of 5 per cent sodium hydroxide and final volume was adjusted so that 1 c.c. of the solution represented 333 c.c. of original urine. The material was centrifuged to separate any insoluble material still remaining. The supernatant fluid, which was now a clear, dark brown solution, was put in sterile bottles and 0.5 per cent phenol added as a bacteriostatic. No infections resulted in the animals injected with this material.

TABLE II

Results Obtained with the Benzoic Acid Extract

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Acute Monocytic Leukemia
Myeloid reaction				
+++	3			
++	2			
+	1	1	1	
±	1	1		1
Erythroblastic	1	1	1	
Negative	4	5	1	1

Extracts prepared by this method were obtained from the urines of patients with chronic myeloid leukemia, chronic lymphoid leukemia, acute monocytic leukemia, and from normal individuals. They were administered to guinea pigs in progressive daily doses of 0.25 c.c. to 1.5 c.c. This extract usually caused death of the animals within two weeks of the beginning of the injections, and the total amount of original urine necessary to produce a positive result was less than that required in other extracts. Extract from only 3.24 liters of urine from patients with chronic myeloid leukemia was sufficient to produce positive myeloid reactions, on the average.

Results obtained with this extract are shown in table 2. Seven of 12 animals receiving the extract of urine from patients with chronic myeloid leukemia showed positive myeloid reactions, five of which were strongly

positive. Two of eight animals given extract of urine from patients with chronic lymphoid leukemia showed weakly positive myeloid reactions as did one of three animals receiving extract of urine from normal individuals. One of two animals receiving extract of urine from a patient with acute monocytic leukemia also showed a positive myeloid reaction. The erythroblastic response was obtained in three animals.

Chloroform Extracts. Method: Urine was obtained from patients with chronic myeloid leukemia, chronic lymphoid leukemia, Hodgkin's disease, acute monocytic leukemia, acute blastic leukemia (type unidentified) and from normal individuals. Insofar as possible, urine from several patients with the same disease was pooled until enough was obtained to make extract for the entire series of animals. In this way, a homogeneous extract was prepared and it was certain that all animals were receiving identical material. Urine was strongly acidified by adding 250 c.c. of concentrated HCl per 1750 c.c. of urine. It was boiled in open beakers for at least 10 minutes to hydrolyze. The hydrolyzed urine was then extracted in a continuous chloroform extractor. Urine flow was adjusted so that about one liter of urine passed through the extractor each hour. The urine entered the lower end of the extraction column and was discarded from the top. The chloroform, after condensing in the reflux type condenser, was broken into small droplets by a fused ground glass disk inserted in the tube which admitted the chloroform to the extraction column. The chloroform collected in the lower end of the extraction column and returned to the flask as a result of the hydrostatic pressure maintained in the extraction column. Practically no difficulty with emulsions was encountered when working with these strongly acid urines.

If the urine was less strongly acid (pH 3.5, for example), emulsions with chloroform were produced which were best broken up by placing a constant temperature water bath (60° C.) around the lower end of the extraction column.

After the urine had been extracted, the chloroform extract was distilled at atmospheric pressure on a water bath to a convenient volume. Usually, 20 liters of urine were extracted with 300 to 500 c.c. of chloroform, and the final chloroform extract was distilled to 100 to 150 c.c. in volume.

This chloroform extract was extracted five times with 50 c.c. portions of 10 per cent sodium hydroxide in order to remove components soluble in strong alkali. This should, theoretically, have removed the acids and phenols, leaving the neutral substances in the chloroform.

The remaining chloroform fraction was placed in a sterile suction flask and enough sterile sesame oil added so that after removal of the chloroform 1 c.c. of the oil preparation was derived from approximately 5,000 c.c. of urine. Chloroform was removed by applying suction to the flask, the incoming air being filtered through a sterile Berkefeld filter. The preparation was dark, reddish brown in color and was not a complete solution. Some of the solid material slowly settled out so that it was necessary to shake the

bottle vigorously before administration. This oil extract contained the chloroform soluble, alkali insoluble fraction of the urine extract.

The five 50 c.c. portions of 10 per cent sodium hydroxide were pooled and the pH adjusted to approximately 1.0 by the addition of concentrated HCl. This caused a heavy precipitate to form. It was evaporated to dryness on a steam bath. The dry material was ground up and extracted five times with 50 c.c. of chloroform. This made it possible to free the mixture of the salt present. The chloroform extract was passed through coarse filter paper to remove particulate matter and the paper washed with small amounts of chloroform until no brown color remained. It was placed in a sterile suction flask equipped with a Berkefeld filter and evaporated to dryness. Enough sterile water and 10 per cent sodium hydroxide were added to adjust the pH to about 8.0 and the final volume so that 1 c.c. represented 200 c.c. of original urine. This fraction contained the chloroform and alkali soluble fractions of the urine.

TABLE III

Results Obtained with the Chloroform Soluble and Alkali Insoluble Extract

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Hodgkin's Disease	Acute Monocytic Leukemia	Acute Leukemia
Myeloid reaction						
+++	1					
++	2					
+						
±	2					
Negative	7	9	7	4	2	1

A. Results with Chloroform Soluble Alkali Insoluble Extract. The oil preparation was given to guinea pigs as shown in table 3. It was administered subcutaneously in daily doses of 0.1 c.c. (representing 500 c.c. of urine) in most instances. A few animals received twice this amount. Injections were continued for eight weeks after which time the animals were sacrificed. Only a very few animals died spontaneously and anemia did not develop. A few of the animals lost weight. Twelve guinea pigs received extract of urine from patients with chronic myeloid leukemia. Five showed positive myeloid reactions and seven were negative. Of these negative animals, three received an extract which had been standing at room temperature for two months. Whether or not deterioration took place cannot be stated, but such a possibility exists. All the animals receiving extracts from sources other than patients with chronic myeloid leukemia were negative. It is noteworthy, perhaps, that this particular extract produced no erythroblastic reactions.

B. Results with Chloroform and Alkali Soluble Extract. The alkali soluble fraction of the chloroform extract was administered subcutaneously to guinea pigs, shown in table 4, in daily doses of 1–2 c.c. (representing 200 to

400 c.c. of original urine). The usual plan was to start with doses of 1 c.c. and increase to 2 c.c. after seven to 10 days. Injections were continued for eight weeks, after which the animals were sacrificed. Several animals receiving the extract of urine from patients with chronic myeloid leukemia died spontaneously before the end of the eight-week period. Some of these animals developed mild anemia and several lost weight.

Six of the 14 animals receiving the extracts from patients with chronic myeloid leukemia showed positive myeloid reactions. Two guinea pigs showed the erythroblastic response and six were negative. Of the animals receiving the extract of urine from patients with chronic lymphoid leukemia, one showed a positive myeloid reaction, two showed the erythroblastic reaction, and 11 were negative. Eleven animals received extract of urine from normal individuals. Four of these showed positive myeloid reactions, one of which was strongly positive, the other three less so but none the less definitely positive. Seven were negative. Of the nine animals receiving extract of urines from patients with Hodgkin's disease, four showed a response which has been listed as "unclassified positive." This reaction differed from those previously described. The organs of these animals contained large numbers of megakaryocytes with an associated cellular reaction consisting of large numbers of blast cells, unassociated with any obvious erythropoietic hyperactivity. Numerous adult eosinophiles were present. This reaction involved especially the spleen, suprarenal gland cortex, and bone marrow. One of the nine animals had a weakly positive myeloid reaction

TABLE IV

Results Obtained with the Chloroform and Alkali Soluble Extract

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Hodgkin's Disease	Acute Monocytic Leukemia	Acute Leukemia
Myeloid reaction						
+++	1		1			
++	1					
+	2	1	2			
±	2		1	1		
Unclassified positive				4		
Erythroblastic	2	2			2	1
Negative	6	11	7	4	2	1

and four were negative. Six other animals receiving urine extract from a patient with acute leukemia, type unidentified, and a patient with acute monocytic leukemia, did not show any myeloid response.

Combined Results. Table 5 is a composite of tables 1 to 4, showing results obtained with different extracts of urine from patients with the specified diseases and from normal individuals. A total of 64 guinea pigs received extracts of urine from patients with chronic myeloid leukemia of which 31 (48.5 per cent) showed definite myeloid hyperplasia and metaplasia.

Twenty-nine animals were negative and four showed the erythroblastic response.

One hundred and four guinea pigs received extracts of urine from individuals not having chronic myeloid leukemia. Of these, only 16 (15.4 per cent) showed any evidence of myeloid reaction. Three of these were strongly positive myeloid reactions, including one animal each receiving urine extract from a normal individual, from a patient with infectious mononucleosis, and from a patient with aplastic anemia.

TABLE V

Composite of Tables 1 to 4, Showing Combined Results Obtained with All Types of Urine Extracts

	Chronic Myeloid Leukemia	Chronic Lymphoid Leukemia	Normal	Hodgkin's Disease	Acute Monocytic Leukemia	Acute Leukemia	Multiple Myeloma	Miscellaneous
Myeloid reaction								
+++	13		1					
++	9							2
+	4	2	5				1	
±	5	1	1	1	1		1	
Unclassified positive				4				
Erythroblastic	4	4	1			1		
Negative	29	26	28	10	7	2		3
Total	64	33	36	15	8	3	2	5

DISCUSSION

We believe these data indicate that urine from patients with chronic myeloid leukemia contains some substance which is capable of producing myeloid hyperplasia and metaplasia in guinea pigs. Extracts of urine from individuals not having chronic myeloid leukemia do not produce a similar response with as great frequency.

Various extraction methods were effective in recovering this substance from urine. Attempts to separate the chloroform extract into alkali soluble and insoluble fractions, using 10 per cent sodium hydroxide, did not result in complete separation, since both fractions contained activity. The alkali soluble fraction produced a greater number of positive reactions, but those animals which showed positive myeloid reactions after injection with the alkali insoluble fraction, did so with extract derived from a smaller amount of urine. It seems likely, therefore, that the methods employed thus far have failed to separate the active substance into any single fraction.

In earlier reports [1, 2] and reports of Miller et al.,[5] it was thought that extracts of urine from patients with chronic lymphoid leukemia produced changes in guinea pigs which could be considered lymphoid hyperplasia and possibly metaplasia. In this series of experiments, however, we have been unable to detect any difference between the results obtained with lymphoid leukemia urine extracts and normal urine extracts. Many of the animals

receiving such urine extracts had spleens in which the follicles were large, spreading, and active, producing an appearance of mild hyperplasia. The extracts of normal urine, however, produce just as much such change as do the extracts of urine from patients with chronic lymphoid leukemia. The lymphoid change present is not comparable in amount to the myeloid changes observed in animals with the myeloid reaction. Any lymphoid hyperplasia resulting in our animals, therefore, does not appear to be specific nor limited to animals receiving extracts of urine from chronic lymphoid leukemia patients. Extracts of urine from patients with the other diseases have not shown any consistent activity so that the results obtained with chronic myeloid leukemia urine extracts appear to be specific.

A few positive myeloid reactions did occur in animals injected with extracts of urine from individuals not having chronic myeloid leukemia. Such positive reactions, however, were not, with one or two exceptions, as marked as those obtained with extracts of urine from patients with chronic myeloid leukemia nor did they occur with as great frequency.

The most reasonable explanation for the occurrence of these "false positive" reactions is that all urine contains some of the substance which is present in larger amounts in urine of patients with chronic myeloid leukemia. Several experimental variables, thus far not controlled, would affect the response of guinea pigs to this substance. These include individual animal susceptibility, variation in the manufacture of the extracts, and variations in individuals from whom the urine was obtained. If a combination of these variables happened to be favorable, it may be expected that a relatively small amount of the substance can produce a positive myeloid reaction.

The substance which produced the myeloid reaction has not been identified. It was recovered by methods known to be capable of obtaining certain of the products of the glands of internal secretion from urine. Androgens, estrogens, adrenal cortical hormone, and pituitary substances can be recovered by one or more of the methods employed. Because the chloroform extraction method is capable of recovering androgens from urine, 12 guinea pigs were given testosterone propionate in varying doses without the occurrence of a positive myeloid reaction. Other guinea pigs receiving whole anterior pituitary extract similarly did not develop myeloid changes.

Whether the substance is a normal metabolic product present in excess in the urine of chronic myeloid leukemia patients or whether it is an abnormal product not normally present in urine remains to be seen. If it is an excess of a normal substance, such excess might be due to overproduction of the substance or to decreased production of some normal neutralizing substance.

Further investigations, aimed at securing a more purified and concentrated product, are in progress so that quantitatively greater reactions can be produced in animals and chemical identification of the substance can be made. Separation of the various extracts into more specific fractions is

being attempted now. In the event that all the activity can be isolated in one fraction, a better understanding of the chemical nature of the substance will be at hand.

Summary

1. Extracts of urine from patients with chronic myeloid leukemia produced myeloid hyperplasia and metaplasia in guinea pigs with much greater frequency than did extracts of urine from patients not having chronic myeloid leukemia.

2. Three different extraction methods and four different extracts are described.

3. The nature of the substance and plans for further investigation are discussed briefly.

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SULFADIAZINE; FURTHER CLINICAL STUDIES OF ITS EFFICACY AND TOXIC EFFECTS IN 460 PATIENTS *

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EVIDENCE for the effectiveness of sulfadiazine in many of the common bacterial infections has now been obtained in several large clinics by a number of observers, all of whom have attested to the relatively low toxicity of this drug.[1, 2, 3, 4, 5] Since the time of our earlier publication on this subject,[2] the use of sulfadiazine at the Boston City Hospital was limited largely to those groups of cases in which additional data seemed desirable. In this paper we wish to summarize the past year's experience with the clinical use of sulfadiazine at this hospital and, in so doing, to bring out a number of points of interest concerning its efficacy and toxicity.

The clinical material comprises 460 patients, none of whom was included in the previous report. Almost all of them were adults treated on the medical wards. For the most part they included patients with streptococcal, staphylococcal and gonococcal infections, the bacterial meningitides and infections of the urinary tract. In such cases sulfadiazine usually was used only if other sulfonamides had not been given for the immediate illness. Sulfadiazine was also used from the start in patients known to have or suspected of having renal impairment, and it was used to continue treatment when toxic effects resulted from other sulfonamides (mostly sulfathiazole) and further chemotherapy was deemed necessary or desirable. All patients who received sulfadiazine for less than 24 hours or a total dose of less than 10 grams are excluded. Most of the latter had mild infections, but a few of them received a small amount of the drug a few hours before death.

The distribution of cases according to age is shown in table 1. A large proportion of the patients were in the higher age groups. One-third of those who recovered and two-thirds of those who died were over 50 years old.

In general, the drug was given orally, beginning with a 4-gram dose followed by 1 gram every four hours, and this was often reduced to 1 gram every six hours after the temperature had remained normal for a day or two. In the cases of meningitis and in some others with severe infections the initial dose was 5 grams of the sodium salt given parenterally, and this was often followed by two or more doses of one-half that amount at suitable intervals

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

This study was carried out with the generous coöperation of the staffs of the various clinical and laboratory services throughout the hospital. The sulfadiazine was supplied by the Lederle Laboratories, Inc.

in an attempt to maintain blood levels between 15 and 20 mg. per 100 c.c. In such patients oral doses were also adjusted to maintain high levels until the infection was completely controlled. Fluids were given liberally, usually about 3 liters a day, and more when the larger doses were used, but it was not always possible to control this factor adequately and probably this accounted for some of the renal complications to be mentioned later. The total dose, of course, varied widely, as shown in table 2. About one-third of the patients

TABLE I

Age Distribution of Patients Treated with Sulfadiazine

Age Group (years)	No. of Cases	Recovered	Died
Less than 20	51	48	3
20–29	63	58	5
30–39	91	83	8
40–49	80	77	3
50–59	73	59	14
60–69	62	50	12
70 and over	40	27	13
Total	460	402	58

TABLE II

Total Dose of Sulfadiazine Used

Dose (grams)	No. of Cases	Died
15–19	42	5
20–29	109	10
30–39	88	3
40–49	73	11
50–74	70	13
75–99	35	5
100–149	22	4
150–249	11	5
250 or more	10	2
Total	460	58

received less than 30 grams, another third got between 30 and 50 grams, and the rest were given larger amounts over periods ranging from 10 days to more than five months.

CLINICAL RESULTS

A summary of the various types of cases treated and a rough estimate of the therapeutic response to sulfadiazine is given in table 3. A few remarks concerning the salient features of each of the groups of cases may be pertinent.

Hemolytic Streptococcal Infections. There were 98 such cases, including two with meningitis (which are listed lower down in the table), but excluding the cases of endocarditis. These cases are of particular interest,

since the clinical data on the effect of sulfadiazine on hemolytic streptococcic infections are notably scant in the reports thus far available.

A favorable therapeutic response was obtained in every one of the 56 cases of erysipelas. Fever and pulse rate returned to normal in almost every instance within 24 to 48 hours after the first dose was given, and this was

TABLE III

Summary of Results of Sulfadiazine Therapy in Various Infections

Infection	No. of Cases	Died	Evaluation of Therapy			Average Dose (grams)	
			++	+	0	Recovered	Died
Hemolytic streptococcal infections							
Pneumonia	6	0	6	0	0	48	—
Tonsillitis, peritonsillitis, etc.	28	0	25	3	0	27	—
Erysipelas (mostly facial)	56	2	52	4	0	25	41
Sepsis	6	1	5	0	1	46	12
Subacute bacterial endocarditis	14	9	1	1	12	106	131
Staphylococcal infections							
Pneumonia	12	0	12	0	0	35	—
Sepsis	5	0	1	4	0	147	—
Friedländer's bacillus infection							
Pneumonia, Type A	2	0	2	0	0	135	—
Pyelonephritis and liver abscesses, Type B	1	1	0	0	1	—	125
Gonococcal infections							
Genital	6	0	6	0	0	58	—
Arthritis: acute	16	0	13	3	0	71	—
Arthritis: chronic	2	0	0	2	0	350	—
Bacterial meningitis							
Meningococcus	11	0	11	0	0	73	—
Meningococcemia without meningitis	4	0	4	0	0	45	—
Pneumococcus	8	5	3	2	3	254	140
Streptococcus	2	0	2	0	0	56	—
Influenza bacillus, Type B	1	0	1	0	0	55	—
Colon bacillus	1	0	1	0	0	20	—
Miscellaneous	4	2	1	0	3	23	30
Urinary tract infections							
Acute	39	1	33	6	0	41	41
Chronic	21	4	3	15	3	84	38
Pneumococcal pneumonia	80	6	66	12	2	42	52
Pneumonia, etiology undetermined	75	12	45	17	13	39	43
Chronic pulmonary infections	26	6	5	8	13	43	52
Miscellaneous infections, not listed elsewhere	34	9	4	17	13	71	59
Totals	460	58	302	94	64		

++ Good therapeutic response attributable to sulfadiazine.
+ Doubtful result or good response with relapse.
0 No apparent beneficial effect attributable to sulfadiazine.

accompanied by rapid improvement in the local lesion. Relapse of infection occurred a week or more after discharge from the hospital in four of the erysipelas patients who had been treated for only three or four days, but all four of them responded favorably to a second course of the same drug. In three patients who failed to respond to several days' treatment with sulfathiazole, a rapid drop in fever and clearing of the local lesion occurred

within 24 hours after the sulfathiazole was withdrawn and sulfadiazine substituted in the same doses. Two deaths occurred in patients in whom the erysipelas lesion was improved. One patient, 62 years old, died of a cerebral hemorrhage two weeks after drug therapy was stopped; the other, 84 years old, died of renal complications of therapy and will be referred to later.

In the six patients with pneumonia, the hemolytic streptococci were obtained from the sputum only, but they were present in large numbers and in repeated specimens as the only significant pathogen. None had a bacteremia. A sterile effusion was demonstrated in one case after several days of treatment. The response in five of these cases was similar to that usually observed in favorable cases of pneumococcic pneumonia. The sixth patient was extremely ill and had definite renal impairment and congestive cardiac failure before treatment was begun. This patient had a stormy course for several days, after which recovery from the infection was complete.

Rapid and complete recovery was also the rule in the 28 cases of severe tonsillitis. These included five cases with a complicating peritonsillar or cervical abscess and four with sinusitis at the time treatment was begun. The six cases of "sepsis" included one with portal vein thrombosis, two with cellulitis and wound infections, and three which followed abortions. One of the latter patients died in less than 36 hours after receiving only 12 grams of drug, mostly as the sodium salt intravenously. In the others the infection cleared rapidly. The general impression was gained that the results of treatment with sulfadiazine in all the cases of hemolytic streptococcic infections were definitely superior to those obtained from any of the other sulfonamides previously used.

Subacute Bacterial Endocarditis. The results of treatment in 14 cases were, on the whole, quite disappointing. The one patient who was apparently cured had rheumatic heart disease, and one blood culture was positive for alpha hemolytic streptococcus before treatment was begun, but there had been no evidence of embolic phenomena. This patient became afebrile directly after treatment, and numerous subsequent cultures showed no growth even after the drug was discontinued. In one other patient, a few negative blood cultures were obtained during therapy but subsequent ones were positive again. No favorable effects of treatment were noted in any of the remaining patients, although the drug was tolerated well in most instances over long periods during which high blood concentrations were maintained. The organism was a beta hemolytic streptococcus in one patient, who died after a week of therapy. In one other patient the streptococcus was identified as an enterococcus belonging to the group D; the rest were classified either as *Streptococcus viridans* or as alpha hemolytic streptococci.

Staphylococcal Infections. *Staphylococcus aureus* infections of the lungs have been seen in this hospital with more than the usual frequency since the outbreak of influenza of 1940–1941.[6] Twelve such cases were treated with sulfadiazine since our previous report.[2] *Staphylococcus aureus* was the only or predominant organism in repeated specimens of sputum from all these

cases and was obtained from blood cultures in three patients. The organism was coagulase-positive in each instance. The response to chemotherapy was rapid in every case and recovery occurred without complications. Only one of these patients received the chemical for more than one week. Sulfathiazole was not used in any of these cases.

Of the five patients with staphylococcus "sepsis," only one became afebrile rapidly after treatment with sulfadiazine and excision of a subcutaneous abscess. Another patient with bacteremia and pyelonephritis improved slowly but continued to have pyuria. The other three continued to have positive blood cultures under full doses of sulfadiazine and their blood was rendered bacteria-free only after surgical drainage of foci of osteomyelitis. In two of the latter cases, longer courses of treatment with sulfathiazole likewise failed to influence the bacteremia prior to operation.

Friedländer's Bacillus Infections. Two patients with severe acute pneumonia whose sputum yielded Type A Friedländer's bacilli in almost pure culture responded to treatment with sulfadiazine with a rapid drop in temperature and marked clinical improvement. The blood cultures were negative in both of these cases. A third patient, not listed in the table, had a fulminating pneumonia and bacteremia with the Type A organism. He died within 12 hours after beginning treatment and less than 48 hours after the supposed onset of his disease. He had received a total dose of 10 grams of sodium sulfadiazine intravenously and 3 grams of sulfadiazine orally without apparent effect on the downhill course.* One patient with pyelonephritis, from whose urine and blood Type B Friedländer's organisms were cultured, had a stormy course and failed to improve under sulfadiazine therapy. In this case the same organism was found in multiple liver abscesses at autopsy.

Gonococcal Infections. The six patients with gonococcal infections of the genital tract all responded to sulfadiazine treatment with a prompt subsidence of fever, symptoms and discharge. Included among them were two patients with epididymitis, two with orchitis, and one with conjunctivitis in addition to the acute urethritis. The sixth patient had cervicitis and salpingitis. There were no relapses noted.

Among the 18 patients with gonococcal arthritis, six also had active genital infections at the same time. Positive cultures were obtained before treatment in every case from the synovial fluid or from the urethra or cervix or both. In 13 of the cases with acute arthritis, fever and the acute joint symptoms subsided within one to five days and did not recur. Three of the acute cases and both of those with symptoms of several weeks' duration responded more slowly and continued to have fever and joint pains with some

* Recently a fourth patient with severe type A Friedlander's pneumonia, with bacteremia and involvement of one entire lung, showed a very good response to intensive treatment with sulfadiazine. Bacteremia and toxemia subsided rapidly, but there was extensive necrosis of a large part of the affected lung which required surgical drainage. The patient improved after the operation, but the ultimate result is still in doubt.

swelling for several days. In five of the patients with acute arthritis, treatment with full doses of sulfathiazole for 10 days or longer failed to bring about improvement, and the fever and joint symptoms subsided within 24 to 48 hours after sulfadiazine was started. In three of these cases, the possibility of drug fever was eliminated by permitting an interval of two or more days to elapse during which fever and arthritis were unabated while no sulfonamides were given.

Bacterial Meningitis. Clinical data concerning the efficacy of sulfadiazine in such cases are also meager, and further information is highly desirable. The cases included here were studied more directly by Dr. Dingle and his associates and only a few high lights of the results of sulfadiazine treatment need be mentioned. There were 27 cases of bacterial meningitis and four cases of meningococcemia without clinical or laboratory evidence of meningitis in which sulfadiazine was the only sulfonamide used. In the latter and in all the 11 cases of meningococcus meningitis, a rapid and complete cure was effected. Similar results were obtained in a three and one-half year old patient with Type B influenza bacillus meningitis, in a five week old infant with colon bacillus meningitis, and in two patients with streptococcic meningitis, one two months and the other four months old. The latter four patients and one of those with meningococcic meningitis were the only patients under 14 years old who are included in this report.

All the eight patients with pneumococcic meningitis received homologous type-specific antipneumococcus serum, usually within eight to 24 hours after sulfadiazine treatment was begun. Three of the eight patients recovered; of these, two were over 60 years old and one had a bacteremia which recurred during treatment. Pneumococcal endocarditis was found at autopsy in two of the cases and was probably present in a third fatal case with rheumatic heart disease on which autopsy was not done. In the other two fatal cases there were extensive fractures of the skull.

The miscellaneous cases of meningitis include one in which no bacteria were identified but the clinical picture and the favorable response to sulfadiazine treatment suggested a probable meningococcal etiology. Two of the other three cases turned out to be tuberculous and the third syphilitic in origin, and no improvement occurred under sulfadiazine therapy.

Urinary Tract Infections. There were 60 patients, in addition to the two already mentioned, who were treated with sulfadiazine for a variety of infections of the urinary tract. The results were essentially similar to those previously noted.[2] In general, the patients with uncomplicated acute infections responded very favorably. Two instances of acute glomerular nephritis of moderate severity are included. They showed definite improvement under treatment.

Almost all of the chronic cases were associated with local surgical conditions or with severe systemic diseases which obscured the results of therapy or tended to maintain the infection. Some of these patients had impaired

renal function with nitrogen retention before treatment was begun. This was definitely improved in most instances during treatment, but in two patients the blood non-protein nitrogen increased. All of these patients required the closest control of their fluid balance and chemotherapy. The deaths among these cases resulted from the underlying local or systemic disease.

Pneumonias. The results of sulfadiazine treatment in the 80 cases of pneumococcal pneumonia which are included here compare favorably in every respect with those previously reported from this and from other clinics.[1, 2, 3, 5] Of the six deaths in this group, five occurred in patients in whom the pneumonia was secondary to a disease which was itself fatal. In the pneumonias of undetermined etiology, the results varied. In about two-thirds of these cases the response to the chemotherapy was comparable to that seen in typical pneumococcal pneumonia, which some of them may have been. Those who failed to show any favorable response to the treatment include a few atypical pneumonias, possibly of virus etiology, and others that were secondary to severe systemic disease. The latter accounted for most of the deaths in this group.

Chronic Pulmonary Infections. These included 26 cases of lung abscess, bronchiectasis, putrid empyema and pulmonary tuberculosis. Five patients in this group showed rapid and marked improvement following sulfadiazine treatment with subsidence of fever and considerable clearing of the pulmonary signs in spite of the underlying chronic lesion. It was assumed that these favorable results were due to the effect of the drug on a superimposed acute pulmonary infection, the etiology of which could not be determined. A few of the remaining patients in this group showed some gradual improvement of pulmonary or bronchiectatic abscesses under prolonged chemotherapy.

Miscellaneous Conditions. These included a large variety of febrile diseases, most of which are not usually considered to be definite indications for sulfonamide therapy. Only two patients in this group are worth mentioning. One was a patient with two large suppurative lesions of actinomycosis, one of the jaw and the other of the lung and thoracic wall. This patient was failing steadily and his disease was extending during several weeks of treatment with sulfanilamide and sulfathiazole, but slow and steady improvement began under intensive and continued treatment with sulfadiazine over a period of five months. The lesions have apparently healed completely and have remained so during the three months since the drug was discontinued.* The second patient had severe Ludwig's angina and showed a dramatic response within 24 hours after beginning intensive sulfadiazine therapy. No radiation or surgery was employed in these two cases.

* Subsequently, however, this patient developed active pulmonary tuberculosis with positive sputa for tubercle bacilli, but actinomyces could no longer be obtained in smears or cultures. The cervical and chest wall lesions remained healed.

Toxic Effects

Untoward symptoms or laboratory evidence of toxicity from sulfadiazine in general were infrequent and mild. Table 4 contains a summary of their incidence and of the average amount of drug received by the patients having each of the various toxic manifestations.

Nausea and vomiting were notably mild and uncommon, and in no instance interfered with continued oral therapy. The 23 patients listed included six who vomited only once, two in whom the symptom may have been due to other causes (over-digitalization in one and mesenteric thrombosis in the other) and two in whom it began during sulfathiazole treatment and continued after sulfadiazine was substituted. In 20 other patients in whom sulfadiazine was substituted because of vomiting from sulfathiazole, the nausea and vomiting subsided promptly. Of interest are six patients with active peptic ulcers who all received a full course of sulfadiazine for various infections and whose gastric symptoms improved during this treatment.

TABLE IV

Summary of Toxic Effects Attributable to Sulfadiazine in 460 Cases*

Toxic Effect	No. of Cases	Per cent	Average Total Sulfadiazine Therapy	
			Grams	Days
Nausea and/or vomiting	23	5.0	49	8
Leukopenia (drop below 4,000)	3	0.7	120	21
Rash with or without fever	7	1.5	62	11
Episcleritis	1	0.2	92	15
Fever alone	1	0.2	40	7
Psychosis (?)	2	0.4	29	5
Urinary tract complications				
Crystalluria only	34	7.4	72	15
Hematuria, all cases	24	5.2	106	17
Gross, with colic	4	0.9	41	6
Microscopic	20	4.3	120	20
With crystalluria	11	2.4	159	27
Without crystalluria	13	2.8	65	11
With oliguria	3	0.7	22	4
Increase in blood nonprotein nitrogen†	6	1.3	94	15

* There were no instances of cyanosis, anemia, purpura,[7] hepatitis, arthralgia, or peripheral neuritis attributable to sulfadiazine.

† Rise of more than 30 mg. per 100 ml. One of these patients had hematuria and is included above.

Leukopenia. One patient with cirrhosis of the liver and jaundice, who received a total of 156 grams of sulfadiazine in 25 days, had a drop of leukocytes from 18,000 to 650 per cubic millimeter with complete absence of granulocytes and with marked thrombocytopenia. In this patient, treatment was continued for five days after the leukocyte count had reached 2400, and the level of free sulfadiazine was 25.6 mg. per 100 c.c. of blood on the day after the drug was discontinued. Recovery was complete following withdrawal of the drug and administration of fluids, transfusions and pent-

nucleotide.* In two other patients the leukocyte count had dropped appreciably at the time the drug was discontinued, namely to 3500 on the seventeenth day in one and to 2500 on the eighteenth day in the other. There were more than 30 per cent granulocytes in both instances and no special treatment was necessary. In five other patients leukocyte counts below 4000 were noted during the first few days of sulfadiazine treatment, but these were attributable to the underlying disease and did not interfere with further chemotherapy.

Drug Fever, Episcleritis and Dermatitis. Drug fever and episcleritis without other manifestations were each encountered in one case. The episcleritis was reactivated after 6 grams of the same drug were given 12 days later. A dermatitis from sulfadiazine occurred in seven patients. It was scarlatiniform in three cases and maculopapular or morbilliform in the others. It was accompanied by a low-grade fever in all but one instance. In one of the patients the rash appeared on the twenty-second day, after 135 grams of the drug, whereas in the others it became manifest between the seventh and eleventh days, after total doses of 35 to 66 grams. In one of the patients in whom a maculopapular rash appeared on the eleventh day, and in another who developed a scarlatiniform eruption on the seventh day of sulfadiazine treatment, this drug was used to continue chemotherapy without interruption after a febrile reaction with erythema nodosum occurred from sulfathiazole. This reaction had completely subsided during the second day on sulfadiazine. Although the latter drug was used in the same manner and with the same or larger total doses in 21 patients having fever and rashes from sulfathiazole therapy, these were the only two among them who also showed the same toxic effects after receiving sulfadiazine.

Nervous and Mental Manifestations. Because of the frequency with which psychoses from sulfadiazine were noted by other observers,[1, 3] this manifestation was looked for particularly. There were only two patients in whom mental symptoms might have been attributable to sulfadiazine. One severe alcoholic patient treated for pneumonia had slight fever and delirium on the seventh day of therapy, but this did not recur when a dose of 5 grams of the same drug was given three days later. A second patient, admitted for smoke inhalation and mild pulmonary infection, was disoriented and confabulated on the third day after receiving 18 grams of sulfadiazine; the total drug concentration in the blood at the time was 16 mg. per 100 ml. The symptoms cleared promptly when the drug was withdrawn. No patient in the present series developed peripheral neuritis from sulfadiazine.

Anemia and Hepatitis. No instance of anemia or hepatitis was noted. On the other hand, six patients with severe liver damage and one with severe hemolytic anemia received doses of from 40 to 156 grams of sulfadiazine without any further deleterious effect on the liver or on the anemia. Indeed, liver function tests indicated improvement in these cases.

* This case has been reported in greater detail by Dr. J. J. Curry.[15]

Complications in the Urinary Tract. These are the most frequent of the significant untoward manifestations of sulfadiazine therapy. They deserve special emphasis not only for that reason, but also because their more serious effects are largely preventable by proper adjustment of the fluid and drug intake.

A large variety of crystals of sulfadiazine and its derivatives, some of which were similar in form to those described by Lehr and Antopol,[8] were noted in routine urine examinations in 34 of the cases without other abnormal findings. Included among them were some patients who had been vomiting and a number who had received alkali (sodium bicarbonate) with each dose of drug.[9] No significance was attached to this isolated finding provided that the urinary output was adequate. In almost all such instances the crystals appeared only after the urine had been permitted to stand at room temperature for several hours, but they were not often seen in the freshly voided specimens.

Hematuria, as evidenced by the finding of a few red blood cells in the microscopic examination of the sediment in routine urinalysis, was noted in 20 patients. In some of these patients the finding may have resulted from previous catheterization or from the underlying disease, as in the cases of bacterial endocarditis. In such instances the hematuria was not accompanied by crystalluria. In one of the patients with blood but no crystals in the urine, there was a marked temporary decrease in urinary output on the third day of sulfadiazine therapy. This patient had had a febrile reaction with urinary suppression and retention of nonprotein nitrogen in the blood from a previous course of sulfathiazole that had ended only five days before the sulfadiazine was given. A second patient had a temporary decrease in urinary output associated with congestive failure, accompanying streptococcic pneumonia.

In four patients, hematuria was associated with costovertebral angle pain and tenderness, or with typical ureteral colic. In two of these patients, one with gross and the other with microscopic hematuria, this was associated with a low fluid intake and with a high concentration of drug in the blood. In both instances hematuria and pain subsided when the fluid intake was increased. A third patient, who had received a course of sulfathiazole therapy without untoward events several months earlier, experienced typical ureteral colic and allegedly passed a stone on the sixth day of sulfadiazine treatment. The calculus was not seen, but there was transient gross hematuria without crystalluria for two days, which then cleared although the sulfadiazine therapy was continued in the same dosage throughout this time and for four days thereafter. The fourth case will be referred to in more detail further on.

It is of interest to note that varying degrees of hematuria were present in 11 of the patients in this series before the sulfadiazine was begun. These included two cases of acute glomerular nephritis. In nine of these cases,

including both of the latter, the hematuria cleared or decreased while the patients were taking full doses of sulfadiazine and maintaining high blood levels. The hematuria did not increase during treatment in the other two patients.

Significant increases in the level of the non-protein nitrogen of the blood occurred during sulfadiazine treatment in five patients who had essentially normal levels to begin with, and in a sixth patient who had a high level before treatment was begun. In one of these patients, who had malignant hypertension, the non-protein nitrogen rose from 40 to 120 mg. per 100 c.c. and the total sulfadiazine level reached 28 mg. per 100 c.c., of which only 7 mg. were in the "free" form. In a second patient, a rise in the non-protein nitrogen from 30 to 67 was accompanied by a rise in the total drug level to 30 mg. per 100 c.c., of which only 13 were "free." In three of the other patients the higher drug level reached was only 18 or less, and only 2 or 3 mg. were in the conjugated form. In fact, in all the chemical determinations of sulfadiazine in the blood in the present series of cases, large amounts of the conjugated form were found only in the two cases cited.

It is of interest here, also, that 14 other patients had high levels of non-protein nitrogen (between 50 and 100) before sulfadiazine treatment was started. In 10 of these cases there was a significant drop in this level, often to normal, during the course of the chemotherapy, whereas in the other four it was not materially affected. In four of these patients the blood concentration of the drug rose to levels between 22 and 40 mg. per 100 c.c., but only a small part of this was not in the "free" form.

A Fatal Case of Urinary Suppression with Colic, Hematuria and Azotemia from Sulfadiazine. One patient died, presumably of a renal complication. Since this was the only fatality attributable to sulfadiazine in the present series, a few of the relevant details in this case may be of interest.

A woman 84 years old was treated with sulfadiazine in the routine manner for facial erysipelas. The fever subsided rapidly and the facial lesion showed marked improvement within two days. The drug was stopped on the fourth day, after the patient had received a total of 22 grams. The non-protein nitrogen on admission was 30. Specimens of urine taken on admission, on the day when the drug was stopped and two days later all revealed no abnormal finding. It was only on the afternoon of the latter day, when the patient complained of definite symptoms suggesting right ureteral colic, that attention was called to the fact that the patient's urine output had been very low. A small amount of "smoky" urine filled with red blood cells and crystals was voided at that time. During the next two days the patient passed only a few cubic centimeters of similar urine and the non-protein nitrogen of the blood rose steadily to 97 mg. per 100 c.c. Cystoscopy and catheterization of the ureters were then carried out, and revealed no obstruction; only a small amount of bloody urine with few crystals of drug were found in the bladder. The drug level at this time was only 2 mg. per 100 c.c. of blood, and two urine specimens each showed a total of only 60 mg. of sulfadiazine per 100 c.c., of which all but 10 mg. were in the conjugated form. Administration of fluids by mouth and parenterally was then of no avail and the patient died on the following day. A few concretions were found in the kidney pelvis at autopsy.

Five other similar cases of urinary suppression under sulfadiazine therapy have already been reported,[2, 10, 11, 12, 13] two of which were fatal.[13] The other three were all in young adults in whom increase in the fluid intake and early ureteral catheterization resulted in complete relief.*

Drug Toxicity in Patients Receiving Multiple Courses of Sulfonamide Therapy

The effect of previous sulfonamide therapy on the toxicity during readministration of the same or related compounds is of great interest, and few data on this subject are available. Lyons and Balberor [14] observed febrile reactions in 36 per cent of patients on readministration of sulfathiazole, but sulfanilamide or sulfapyridine did not precipitate a fever when given after sulfathiazole. They did, however, observe some patients who had early sulfathiazole fever after having previously been treated with one of the other two drugs. Since a large number of the patients in the present series had more than one course of sulfonamide therapy during the same or on separate admissions, the toxic effects from the sulfonamides in these cases will be reviewed briefly.

Readministration of Sulfadiazine. Fifteen patients in this series each received two courses, and six received three courses of treatment with sulfadiazine. The average total dose was 48 grams given in about eight days during the first course, 58 grams in 11 days during the second, and 42 grams in seven days during the third. The average interval was 12 weeks between the first and second courses and three and one-half weeks between the second and third courses. Except for transient microscopic hematuria during the first course in one instance, no toxic effects from sulfadiazine were noted.

Among these 21 patients, 10 had also been treated with sulfathiazole: 5 once, 4 twice and 1 on three occasions. In the latter five patients the courses of sulfathiazole were alternated with those of sulfadiazine. One had a rash and fever from a single and initial course of sulfathiazole; another had a rash and fever during the second course of this drug; and in three others it gave rise to nausea and vomiting each time it was taken. In addition, one of these patients developed a severe anemia during an earlier course of sulfanilamide and another had intense vomiting during a previous course of sulfapyridine therapy.

Sulfadiazine in Patients Who Had Other Sulfonamide Drugs Without Toxic Effects. Thirty-six patients in the present series received a course of another sulfonamide drug without untoward effects during the same or a separate hospital admission. In 25 cases it was given before and in 11 cases after the course of sulfadiazine. Sulfapyridine was used in two, sulfanilamide in five, and sulfathiazole in 29 cases, and one of the latter received

* Two further cases of urinary suppression have been reported since this paper was submitted. One of them required nephrostomy [16] and the other recovered after ureteral catheterization.[17]

two courses. The total dose of these drugs varied from 15 to 600 grams, but it was less than 35 grams in most instances. The average dose of sulfadiazine in these cases was 69 grams, given in 12 days. The interval between the courses of the drugs was one week or less in 20 cases and varied from four weeks to four years in the others. One of the patients had a rash and fever from sulfadiazine on the ninth day after receiving 56 grains; another had crystalluria; and a third, already noted, had hematuria and ureteral colic and presumably passed a calculus during the course of sulfadiazine therapy.

Sulfadiazine in Patients Who Experienced Toxic Effects from Other Sulfonamides. In addition to the various cases already mentioned, 14 patients who received sulfadiazine had a febrile reaction, with or without a rash, from some other sulfonamide drug within 10 days to two years. These included three who had a rash and fever with each of two courses of sulfathiazole; one who had fever alone during one course and a rash during another, both with sulfathiazole; three who had a rash only during the second of two courses of this drug; one who had a febrile reaction from two different courses of sulfanilamide and a rash after a course of sulfathiazole; one who had a moderate anemia from sulfanilamide on one occasion and a rash from sulfathiazole on another; and one who had a scarlatiniform rash from sulfanilamide. Almost all of these patients received 30 grams or more of sulfadiazine without toxic effect beyond a transient microscopic hematuria in two cases.

Complications in the urinary tract from other sulfonamides, mostly sulfathiazole, were noted in 17 of the patients. Three of them had nitrogen retention of significant degree, eight had hematuria, and six had crystalluria. One of these patients had a diminished urinary output during sulfadiazine, but none of the others showed any toxic effects from the latter drug.

Two additional patients had severe anemia during sulfanilamide treatment more than one year prior to receiving sulfadiazine, and 17 others had nausea and vomiting during treatment with sulfapyridine or sulfathiazole, or both, more than one month previously. Among the latter, one experienced nausea, another had oliguria and slight hematuria, and a third had a rash during treatment with sulfadiazine.

Summary and Conclusions

The results of treatment with sulfadiazine in 460 patients with a variety of infections are presented. These are in addition to the 446 patients previously reported from this hospital. The earlier conclusions concerning the efficacy and low toxicity of sulfadiazine have been confirmed and extended.

In particular, the additional data presented suggest that sulfadiazine may be accepted as the drug of choice in all cases of hemolytic streptococcic infections and in all of the various acute bacterial meningitides.

The accumulated clinical results in the cases of acute gonococcal and staphylococcal infections and in the acute infections of the urinary tract suggest that the efficacy of sulfadiazine in most of these cases is probably similar to that of sulfathiazole. Because of its lower toxicity, however, sulfadiazine may be considered to be the drug of choice, particularly when prolonged therapy is desirable.

The present results, taken together with others reported,[1, 2, 3, 5, 6b] seem to justify the claim for sulfadiazine as the drug of choice for initiating chemotherapy in all cases of acute pulmonary infections and for continuing treatment in such cases when they are caused by pneumococcus, streptococcus and probably also staphylococcus and Friedländer's bacillus.

Toxic effects attributable to sulfadiazine were relatively few and mild. The comparatively frequent occurrence of complications in the urinary tract warrants the exercise of caution in the control of the dosage of the drug in relation to the fluid intake and output. This is particularly essential in old persons, in patients with hypertension, and in every patient who may have some impairment of renal function. With adequate control, this drug may be administered so as to produce therapeutically effective blood levels wherever indicated, even in many patients with severe renal disease. When oliguria occurs, the fluid intake should be increased promptly or the dose of drug reduced, depending on the circumstances. If there is marked or complete suppression of the urine output, particularly when accompanied by ureteral pain, fluids should be forced and ureteral catheterization should be employed early if a fatal outcome is to be avoided. A fatal case of urinary suppression with ureteral colic, hematuria and azotemia is reported.

The occurrence of agranulocytosis after prolonged therapy in one case suggests that, regardless of how infrequent this complication may be, it must be looked for in all patients undergoing sulfadiazine treatment for two weeks or more. Early recognition, with prompt withdrawal of the drug, will probably avoid fatalities from this complication.

Full courses of sulfadiazine have been used in a considerable number of patients who had previously been treated with sulfonamide drugs. The toxic effects from sulfadiazine in these cases were apparently similar in frequency and in all other respects to those seen in patients who had no previous experience with other sulfonamides. This was true regardless of whether or not the patients had experienced toxic effects from the latter.

No evidence of "sensitization" was noted in any of the 21 patients who received a second or third course of sulfadiazine. In most of these cases full doses were used for a week or more each time. Some of them had also received one or more courses of other sulfonamides, with or without toxic effects. The possibility of sensitization, however, has not been excluded. Episcleritis was reactivated on early readministration of sulfadiazine in one case. Other instances of rashes and febrile reactions reappearing when the drug is given again after a brief interval have also been known to occur, although they were not encountered in the present cases.

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CONTROL OF THE HYPERGLYCEMIA OF OBESE "DIABETICS" BY WEIGHT REDUCTION *

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THREE years ago we [1] reported the favorable effect of weight reduction upon the hyperglycemia of obese middle-aged persons. We are now in a position to deal with a still larger material. The effect of reduction of weight upon the delayed utilization of glucose displayed by 62 obese adult men and women forms the substance of this paper. A number of the patients had been referred to the Diabetic Clinic by their physicians because diet and insulin had failed to abolish the glycosuria. Others came to the hospital because they were suffering from pruritus vulvae, cataract, gangrene, gall-bladder disease or merely the fatigue and breathlessness which often accompany obesity. A few of these latter patients knew that the urine had contained sugar for many years. Others had been told that they were diabetic within the recent past. Still others were unaware of the glycosuria until it was noted as part of the routine examination in the hospital. The youngest patient was 27 years of age, the oldest 71 years. The average age of the group was 52 years, and the ages of two-thirds of the patients ranged from 42 to 62. Usually the obesity was not extreme.[1] Two-thirds of the patients were less than 40 per cent overweight. The distribution of the excess weight is shown in table 1. Two-thirds of the patients were females.

TABLE I

Distribution of Excess Weight

Per Cent Overweight	No. of Cases
10– 20	5
20– 30	20
30– 40	14
40– 50	8
50– 60	8
60– 70	2
70– 80	1
80– 90	3
90–100	1
Total	62

Since many investigators, including ourselves,[2] have shown that restriction of dietary carbohydrate results in delayed utilization of glucose, each patient was placed on a standard preparatory diet containing 300 grams of carbohydrate, 80 grams of protein, and approximately maintenance calories for three or more days before the glucose tolerance test was performed. This was important since a number of the patients had been following low

* Read at the St. Paul meeting of the American College of Physicians April 23, 1942.

carbohydrate diets as part of the treatment of the diabetes. Others had been eating little because they were ill. The glucose tolerance test was performed in the usual manner, giving 1¾ grams of glucose per kilogram of ideal body weight.

The next day, the reduction diet was begun. From then on, the glycosuria was ignored. Insulin was not administered. The patient was prepared for each subsequent glucose tolerance test by feeding the standard preparatory diet containing 300 grams of carbohydrate for five days preceding the test.

The patients need to be separated into two groups in order to judge of results. The first group consists of 47 patients who adhered to the diets

TABLE II

A

Little or No Improvement by Reduction of Weight to Normal

Case No.	Age	Normal Weight	First Test					Second Test				
			Wt.	F.	1 Hr.	2 Hr.	3 Hr.	Wt.	F.	1 Hr.	2 Hr.	3 Hr.
	Yrs.	Lbs.	Lbs.	Mg. %	Mg. %	Mg. %	Mg. %	Lbs.	Mg. %	Mg. %	Mg. %	Mg. %
209133	58	131	165	300	400	410	370	135	272	374	416	410
451014	43	138	180	270	452	468	480	136	370	524	588	628
407412	46	136	162	186	374	428	404	137	172	292	332	270
284756	52	123	144	252	410	500	480	130	240	306	384	374
474714	71	145	168	245	374	472	482	150	176	290	306	296
140536	41	128	158	264	404	495	602	131	186		360	284

B

Slightly Abnormal Glucose Tolerance Tests after Weight Had Become Normal

400526	45	145	181	124	278	266	176	149	87	200	188	88
422552	61	125	159	254	434	432	378	129	102	220	242	148
412441	42	125	160	258	352	500	340	129	118	190	160	138
414080	57	137	165	176	300	272	214	137	102	242	142	118
373000	62	127	152	152	278	300	278	124	102	208	133	88

prescribed by us as long as we requested them to do so. The second group of 15 patients adhered to reduction diets until they had lost a significant amount of weight, but even though their glucose tolerance tests were still abnormal, they refused to reduce further.

Returning now to the 47 patients who coöperated fully, reduction of weight to normal caused little or no improvement in six of them (12.6 per cent). Their responses are shown in table 2 A. Another five (10.6 per cent) were strikingly improved by reduction of weight to normal. The increase in the ability to dispose of glucose by these patients may be seen in table 2 B which compares the glucose tolerance tests before and after reduction of weight. Further evidence of the marked improvement is had in the fact that diets containing 300 grams of carbohydrate caused neither glycosuria nor abnormally high fasting blood sugars. Each of the remain-

ing 36 patients (76.6 per cent) achieved normal glucose tolerance tests after weight reduction of varying amounts. The tests had become normal in six of these 36 patients when they were still 28 to 45 per cent overweight. However, they had lost 35 to 76 pounds by this time. The remainder of these 37 patients had to continue to reduce their weights to within a few pounds of normal or to fully normal in order to be able to dispose of glucose normally. Mrs. G. C. is an example of how reduction of weight to normal, followed by adherence to that weight, finally made it possible for her to dispose of glucose in an entirely satisfactory manner. Her normal weight was 127 pounds. On February 12, 1940, she weighed 160 pounds and the test was:

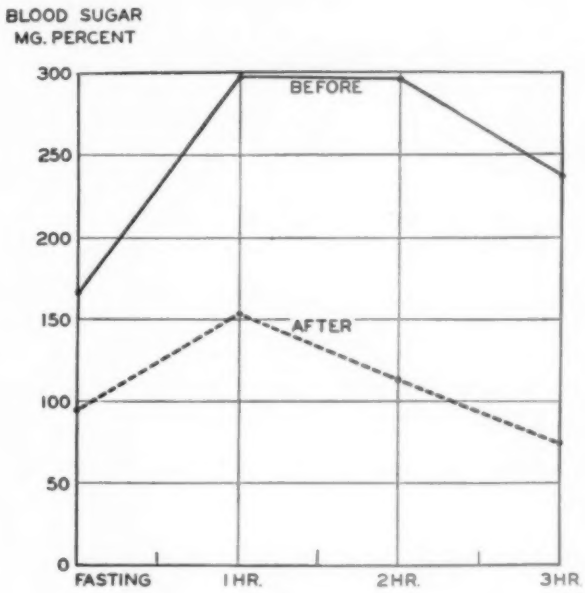

FIG. 1.

fasting, 182; first hour, 292; second hour, 244; third hour, 250 mg. glucose per 100 c.c. blood. On July 5, 1940, when her weight was 134 pounds, the blood sugar readings during the test were: 116, 216, 256, 150. Her weight was 129 pounds on October 14, 1940, and the glucose tolerance test was as follows: 124, 168, 145, 103. One year later, when her weight was the same, the blood sugar readings during the test were 87, 133, 112, 107.

The mean blood sugar readings during the glucose tolerance tests performed before treatment and again when they had become normal after weight reduction are portrayed in figure 1. The distribution of the blood sugar levels during the tests performed before and after weight reduction in these 36 patients is shown in table 3. The effect of weight reduction upon the blood sugar readings obtained in the third hour of the tests is of special interest because the values are so low. Most of them are less than 75 and

five of them are less than 50, suggesting that weight reduction had enabled these patients to dispose of glucose at a supernormal rate.

The 15 patients who coöperated partly gave clear evidence that disposal of glucose can be greatly increased by reduction of weight. For example, the patient whose initial glucose tolerance curve was the highest in this group, made the following response to weight reduction. Her normal weight was 133 pounds. Before treatment she weighed 173 pounds and the blood sugar readings of the test performed at that time were: fasting, 212; first hour, 348; second hour, 356; third hour, 500. When her weight had been brought down to 143 pounds, the test gave the following blood

TABLE III

Distribution of Blood Sugars during Glucose Tolerance Tests Performed before and after Reduction of Weight in 36 Patients Whose Tests Became Normal

Blood Sugar	Fasting		First Hour		Second Hour		Third Hour	
	Before	After	Before	After	Before	After	Before	After
Mg. %	No.	No.	No.	No.	No.	No.	No.	No.
25- 50								5
50- 75		4				2		18
75–100	1	22				10	1	8
100–125	8	10		4	1	12	2	5
125–150	9			14		11	3	
150–175	7			13		1	4	
175–200	3		3	5	5		4	
200–225	2		5		3		3	
225–250	2		4		5		2	
250–275	1		1		4		4	
275–300	1		9		4		1	
300–325	2		5		3		6	
325–350			4		2		2	
350–375			2		4		1	
375–400			1		1			
400–425					1		1	
425–450							2	
450–475					1			
475–500								
500–525			1		1			
525–550			1		1			

sugar values: 125, 217, 200, 208. She refused to reduce further. The distribution of the blood sugar values obtained during the glucose tolerance tests performed before and after partial reduction of weight of these 15 patients may be seen in table 4.

Table 5 permits a comparison of the glucose tolerance tests in the several groups of patients. Among the 47 patients who coöperated fully, the sub-group who responded best to weight reduction had the lowest tests, and the sub-group that did not improve had the highest initial test. This suggests that the height of the initial test may be useful as an indicator of the response to reduction. If this is true then the position of the average initial curve from the 15 patients who coöperated only partly permits the prediction

that many of them would have been able to give normal tests if they had lost more weight.

TABLE IV

Distribution of Blood Sugars during Glucose Tolerance Tests Performed before and after Partial Reduction of Weight in 15 Patients

Blood Sugar	Fasting		First Hour		Second Hour		Third Hour	
	Before	After	Before	After	Before	After	Before	After
Mg. %	No.	No.	No.	No.	No.	No.	No.	No.
50– 75								1
75–100		4						1
100–125	1	6					1	5
125–150	3	4		1				1
150–175	3	1		2		3	1	1
175–200	3	1		2		5	1	3
200–225	1			4		1	2	2
225–250	3		2	3		2	2	
250–275			2	2	3	1		
275–300	1		1	1	2	3		1
300–325			2		1		2	1
325–350			3		1			
350–375			3		2	1	2	
375–400					1		1	
400–425					2			
425–450			1		1		2	
450–475			1					
475–500					1		1	
500–525					1			
525–550								

TABLE V

Glucose Tolerance Tests on 62 Patients before and after Weight Reduction

		Before				After			
		F	1	2	3	F	1	2	3
Full Coöperation	36 Patients. Glucose Tolerance Tests became normal.	163	293	292	234	89	154	113	75
	5 Patients. Tests became markedly improved.	193	328	390	277	102	212	173	116
	6 Patients. Tests slightly or not at all improved.	253	402	462	469	231	349	393	366
	These 47 Patients' Averages	177	310	323	268	110	184	154	116
Partial Coöperation	15 Patients. Tests improved.	189	330	364	284	119	218	215	157
All	62 Patients. Averages	180	315	339	272	112	192	169	126

But even if no assumptions about the outcome, had each patient cooperated fully, are made, the weight reduction of these 62 hyperglycemic patients still caused 57 per cent of them to dispose of glucose normally. Another 33 per cent showed improved ability to dispose of glucose. Only 10 per cent were not improved. Analysis of the results obtained with the 47 patients who coöperated fully showed that 77 per cent of them became able to dispose of glucose normally.

Twelve of the patients whose tolerances became normal avoided gain of weight, and the glucose tolerance tests were repeated 6 to 29 months after the first normal tests were obtained. Each of the last tests was normal also. Since these patients had been eating the usual mixed diet in the interval between the first and last normal test, the benefit from the reduction diets, which were necessarily restricted in carbohydrate as well as fat to lessen the caloric intake, cannot be attributed to the carbohydrate restriction.

Discussion

Other writers who have dealt with the relationship between obesity and delayed utilization of glucose have taken it for granted that the patients were diabetic. By definition they would be suffering then from an hereditary incurable disease of the Islands of Langerhans that prevented them from forming normal amounts of insulin. We are contending that the delayed utilization of glucose encountered in obese adults is usually of a fundamentally different nature for these reasons: (1) The disturbance is mild, often so mild that it may exist for many years without causing symptoms even though it is not treated. Clinical acidosis does not occur. (2) Delayed utilization of glucose is a common accompaniment of obesity. Thus Kisch [3] found that about 50 per cent of all markedly obese persons were glycosuric. Paullin and Sauls [4] reported that 58 per cent of 26 obese persons who were aglycosuric gave abnormally high glucose tolerance curves. John [5] performed glucose tolerance tests on 182 aglycosuric obese patients and found that 65 per cent of them were unable to dispose of ingested glucose at the normal rate. Ogilvie [6] concluded that the impairment of tolerance was related to the duration, not the degree of obesity. It took more than 11 years of obesity to cause delayed disposal of glucose. On the other hand, every woman who had been obese more than 18 years, showed delayed utilization of glucose. These investigations indicate that prolonged obesity usually causes changes in the organism, one of whose manifestations is delayed utilization of carbohydrate. (3) Those who would still contend that these obese hyperglycemics are diabetic and that their inherent pancreatic weakness is accentuated by the obesity, would necessarily have to assume that the majority of persons are diabetic. Are they willing to do so? (4) If our patients are mild diabetics whose inherited weakness becomes clinically apparent when their total metabolism is increased by the obesity, then those whose inherent fault has become hidden again through reduction of weight

should manifest their diabetic state when they suffer from an infection. Since we have had only one opportunity to observe this condition, we can do no more than report that Mrs. S., whose glucose tolerance had become normal through reduction of weight, subsequently was admitted to the hospital one week after the onset of an upper respiratory infection of increasing severity. Her temperature on admission was 104° F.; she had pain in the chest and was raising bloody sputum. Nevertheless, the urine was sugar free. (5) If the severity of diabetes is augmented by increasing the weight of the patient, it should be possible to demonstrate this effect in the juvenile diabetic. We have made this attempt. Miss B. is a young woman who presents the classical picture of severe diabetes. When she weighed 101 pounds she was placed on a diet that contained 300 grams of carbohydrate and 2800 calories for five days, and she received no insulin. During the three last days the 24 hourly urinary glucose averaged 211 grams; and the glucose tolerance test performed the next morning was: fasting, 264; first hour, 484; second hour, 516; third hour, 432. Four months later when her weight had increased to 132 pounds, she was placed on the high carbohydrate diet again, without insulin. The 24 hourly excretion of glucose averaged 209 grams this time and the glucose tolerance test was 286, 444, 465, 500. A gain of 31 pounds did not lessen her ability to dispose of glucose.

It will be recalled that a few of our obese hyperglycemics were not improved by reduction of weight to normal. One explanation is that they are individuals who are victims of diabetes of the juvenile type. It is also conceivable that the prolonged hyperglycemia caused organic changes in the Islands of Langerhans, since Best [7] has shown that high blood sugars do damage the insular cells in dogs.

During the year 1936, 370 new cases were classified as diabetic after thorough study. Three hundred and sixteen of them were 30 or more years old, and 57 per cent of these adults were obese on admission. Therefore, approximately one-half of these 370 patients, whose ages ranged from a few months to 71 years, were obese when they were admitted. Our experience has shown that adequate reduction of weight will abolish all evidence of lessened utilization of carbohydrate in at least 60 per cent of adult obese hyperglycemics. Since one-half of all the new cases classified as diabetic were obese, it is permissible to predict that thorough-going reduction of weight of the obese members of the group will abolish the retarded utilization of glucose in one third of the patients who are believed to be suffering from diabetes mellitus.

Conclusions

The glucose tolerance tests became normal in 77 per cent of those adult obese hyperglycemic patients who were willing to undergo adequate weight reduction. Reasons have been given to support the belief that these persons

have not inherited an incurable disease of the tissues that produce insulin. We explain the hyperglycemia as a manifestation of obesity.

The normal or ideal weight of an adult human being cannot be stated with great precision. The figures compiled by the large life insurance companies are closest to the ideal for the present, even though the weight and height were obtained on clothed persons who had not removed their shoes and who were postprandial. Details may be obtained by consulting Fisk's book "Health Building and Life Extension," 1923, Macmillan Co., New York.

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THE CLINICAL SIGNIFICANCE AND TREATMENT OF PYURIA*

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THE physician of today, whatever may be the nature of his practice, must know something about progress in all fields of medicine. Much progress has been made in recent years in knowledge concerning infection in the urinary tract. It is appropriate, therefore, to discuss before internists some of the clinical phases of urinary infection and its treatment. I take it for granted that most patients who come to the internist have symptoms other than those referable to the urinary tract, and that pyuria, when present, is discovered in the course of routine urinalysis. If it were otherwise, the modern sophisticated patient probably would consult his neighborhood urologist first. It should be said at the outset, however, that urologists look with some doubt on those who intrude in their field but do not belong to the guild. But then, since pyuria is a complication which may be common to patients who consult specialists in any field, including that of the internist, urologists are glad to reveal the secrets underlying recognition and treatment of it, up to a certain point.

Once pus cells have been found in the voided urine, what is their clinical significance? To begin with, it should hardly be necessary to state that pus cells found in voided urine may not have originated in the urinary tract. In most cases pus cells found in the voided urine of a *female* patient are absent in the catheterized specimen of urine from the same patient. The finding should *invariably* be checked by catheterization. I have seen many patients referred for urologic investigation because of persistent pyuria who never would have been sent had they been catheterized. When catheterization is inadvisable or impossible, a satisfactory specimen of urine can be obtained by careful cleansing of the external portion of the urethra and by spreading the vulva while voiding. Pus cells in the voided specimen of urine of the male patient, on the other hand, are of definite significance, particularly if the two-glass test is used and if the urine in the second glass is found to contain pus. If, however, the pus cells are found largely in the first glass, infection in the urethra secondary to chronic prostatitis must be suspected. In fact, the presence of a variable number of pus cells in the urine of a male adult usually is caused by some form of what Keyes has called "prostatism."

Patients may be observed who complain of several things, among them frequent micturition. On examination of their urine no pus cells may be found. These patients offer a clinical problem, even to the urologist. Most of them are women in the fifth and sixth decades. In many cases the symp-

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toms are caused by a chronic cicatricial type of urethritis which may cause little or no pyuria. Bacteriuria occasionally is observed without pyuria, and can be the cause of vesical distress. Interstitial cystitis may be the cause of frequent micturition and dysuria with little or no pus in the urine. The patient may have been told that vesical irritation is caused by pressure of adjacent pelvic organs. The truth is that pressure by intrapelvic lesions seldom causes frequent urination or dysuria. Rarely, allergy may explain some instances of vesical irritation. In some cases no etiologic factor may be found, even after a careful search, and the symptoms can be explained only on a functional basis—the so-called irritable bladder. An organic lesion is present somewhere in the urinary tract in most cases, and a careful urologic examination is indicated.

Merely to report the presence of pus cells in the urine, however, is of little clinical value. It is of equal importance to know whether any bacteria are present and if they are, what kind. Rough identification of bacteria can be made by means of Gram's staining of the urinary sediment. This simple method can be employed easily by any laboratory technician, and should be made a part of routine urinalysis. Cultural methods may be indicated for further identification of bacteria, but for most clinical purposes they are unnecessary.

If there is any advance in medical science to which the urologists have contributed in recent years, it is an increase in the knowledge concerning those bacteria involved in infection of the urinary tract. Only a few years ago many urologists scarcely knew the difference between a bacillus and coccus when they saw them under the microscope. Today they glibly quote the names of every bacterium ever heard of, and are familiar with many of the cultural characteristics of bacteria. In order to treat urinary infection intelligently a working knowledge of its bacteriology is essential. It will not avail to dust off your old textbooks on bacteriology, since present knowledge of the subject has been greatly revised and it will be necessary to consult current literature to bring yourself to date.

It is well known that the bacteria most commonly found in infected urine are either the lowly colon bacillus or the more tenacious relatives of that organism, the *Aerobacter aerogenes* and the *Pseudomonas aeruginosa*. Some observers would like to link the origin of the colon bacillus with the adjacent intestinal colon. The contention is that colonic stasis is a factor, and that it permits the colon bacillus to permeate the urinary tract. This never has appealed to me as being logical. Constipation or colonic stasis seldom causes urinary infection, to my knowledge. If it were a common factor, sulfaguanidine should control bacillary infection in the urinary tract, but it has proved to be much less effective than any of the other sulfamido drugs.

Among other gram-negative organisms frequently observed in infected urine are included members of the genuses Proteus, Pseudomonas and Salmonella. These organisms are urea-splitters and, as a result, the urine often becomes alkaline, with resulting deposition of calcium on the inflamed

mucosa of the bladder or in the kidney. These bacilli may be exceedingly difficult to eradicate, even with recently discovered chemotherapy. Among the gram-positive cocci, micrococci are most commonly observed. They usually are present in the urethra and are comparatively innocuous, although occasionally they may become virulent. Staphylococci are not commonly found in the urine but, when present, can be virulent formers of abscesses. Often they are associated with formation of calculi. Streptococci seldom are the active agents in urinary infection, except in the form of the *Streptococcus faecalis*. This bacterium usually is a secondary invader, after primary infection in the urinary tract, and usually is found in mixed infections. Unless its presence is detected, it may be the cause of persistent infection after the bacilli have been eliminated. Many patients with pyuria are observed in whom a careful search for bacteria, both by Gram's staining of the urinary sediment and by culture, reveals none. This may be difficult to explain, but bacteria may be present which are so few in number and have become so attenuated that it is difficult to discover them by the usual methods of investigation. The theory of amicrobic pyuria has been advanced, but it does not seem to have a logical basis. Some of these patients will respond to chemotherapy without the organisms being found.

The possibility of tuberculosis must be considered in every case of persistent pyuria unless it is proved not to be present. There has been a decided change in the clinical picture of patients with renal tuberculosis in the last decade or two. It is evident that a relative immunity to the disease has been developed in this country. The patient of 30 years ago complained of severe dysuria and urinary frequency; many pus cells were found in the urine and the diagnosis was made with comparative ease. Its clinical recognition today may be exceedingly difficult. The symptoms usually are slight; only a few pus cells may be found in the urine, and on cystoscopy the bladder may appear normal. The usual carbolfuchsin staining of the sedimented urine should be done coincident with Gram's staining. The presence of the *Escherichia coli* in the sediment should not lead one to exclude tuberculosis, however, since it may be coincident in the urine with the *Mycobacterium tuberculosis*. If there is anything suggestive of tuberculosis in the course of physical examination, or if pyuria is not eliminated by chemotherapy, the urine should be examined for the *Mycobacterium tuberculosis* and a more sensitive method of staining (with auramine) should be used. Experience with this new stain has shown that it will detect the presence of the *Mycobacterium tuberculosis* in the urinary sediment much more often than will carbolfuchsin stain. In case of doubt inoculation of guinea-pigs remains the most nearly accurate test, and should be employed. Cultural tests for tuberculosis, although satisfactory in the hands of some, do not have the accuracy of inoculation of guinea-pigs. Treatment of this type of tuberculosis can be summarized by regarding the lesion as unilateral from a surgical standpoint, and bilateral from its postoperative aspect. Postoperative medical supervision is of primary importance in the postoperative

result. Chemotherapy is of no value unless there is a secondary bacillary or coccic infection in the bladder. When pyuria persists after nephrectomy, this possibility should be considered.

Although patients usually come to the internist primarily because of lesions in various organs other than the genitourinary tract, not infrequently their condition is complicated by the presence of a variable degree of urinary infection. In the surgical field pyuria probably is most often observed in the presence of lesions in the gall-bladder, the thyroid gland, the gastrointestinal tract and the pelvic organs. The questions usually asked by my colleagues in clinical diagnosis are: (1) What is the source of the pyuria? (2) Can its treatment be delayed until the major lesion is taken care of? and (3) Will the urinary infection interfere with surgical treatment of the primary lesion, if operation is indicated?

At the clinic it has been our experience that urinary infection seldom interferes with surgical treatment unless symptoms are present which indicate acute or severe lesions in the urinary tract. Provided renal function is normal, the existence of mild chronic pyelonephritis or cystitis seldom causes difficulty after operations for lesions in other organs. It would hardly be advisable, however, to proceed with surgical treatment of the primary lesion without knowledge of at least something about the source of the pyuria. It should be determined whether or not urinary obstruction exists or whether there is a renal lesion which might seriously interfere with operation. Occasionally, the lesion in the urinary tract may require treatment before therapy can be directed to the patient's major condition.

Probably the more common medical conditions with which pyuria may be associated are diabetes and circulatory lesions. Urinary infection formerly was a rather frequent complication of diabetes but, since the advent of insulin, it is observed much less frequently in such association. When pyuria is present in such a case it usually is caused by mild bilateral pyelonephritis and cystitis. Unless some underlying lesion is present in the urinary tract, this type of pyuria should respond to intelligently conducted chemotherapy, although in some cases of diabetes the infection is unusually resistant. Occasionally, a few pus cells are found in the urine in cases of glomerulonephritis, and the presence of a complicating or etiologic infectious element may be inferred. In fact, in some cases in which a variable number of pus cells are present in the urine it may be difficult to determine whether or not the nephritis is primarily of infectious origin. In such cases it would be desirable to search for bacteria and to visualize the urinary tract in the excretory urogram for evidence of deformity in the renal pelvis or calices. In the treatment of these patients the presence of possible foci of infection should be carefully determined; and, if foci are found, they should, of course, be eliminated.

It should be unnecessary to say that in every case of urinary infection without apparent cause a careful search should be made for foci of infection. This search should include roentgenograms of teeth, examination of tonsils

for hidden crypts, and evidence of infection in the prostate gland, or the cervix and vagina. Incidentally, it should be remembered that tonsils or teeth may infect the prostate gland, which in turn may be the immediate source of cystitis or of ascending pyelonephritis. The removal of such foci may be far more efficacious in overcoming infection than chemotherapy. It would seem logical to suppose that chronic infection in any organ might act as a focus for infection in the urinary tract. Clinical experience, however, does not definitely corroborate this. However, acute infections involving various organs not infrequently are complicated by infection in the urinary tract. I have observed many patients with urinary infection coincident with acute or subacute cholecystitis in whom the urinary infection disappeared after removal of the infected gall-bladder. On the other hand, the incidence of cholecystitis among patients who have chronic pyelonephritis is no greater than the average.

A question often discussed is, what is the significance of pyuria in cases of hypertension? In view of the general acceptance of the theory that a unilateral renal lesion can be an etiologic factor in hypertension, this question assumes major importance. It has been my experience that there are very few patients suffering from hypertension resulting from a unilateral renal lesion who have no pus cells in the urine, or a history of previous urinary infection. It is true that some patients with atrophic pyelonephritis have very few pus cells and that the urinary symptoms of such patients may be obscure. It is evident that in every case of hypertension with pyuria thorough study should be made of the urinary tract. Unfortunately, the percentage of patients suffering from hypertension with unilateral renal lesions is limited, and the percentage of those who are permanently relieved by nephrectomy is even more limited. Nevertheless, the occasional patient who is cured by nephrectomy makes intensive search for this particular condition worth while. Although at the Mayo Clinic we do not make routine urographic studies for every patient who has hypertension, it is advisable to do so for all patients who have urinary infection or have had it, and also for those who previously have undergone a renal operation. Why renal infection is only occasionally an etiologic factor in hypertension probably was best explained by Page, who stated that renal pathology such as that resulting from infection is of importance only if the intrarenal pulse pressure is disturbed.

Having determined that the pyuria persists in the catheterized specimen of the female patient or in the voided second glass in the male patient, and having carried out simple Gram's staining of the urinary sediment in order to get a rough estimate of the bacteria present, and having excluded an obstructing or infected prostate gland as the source, what next should the internist do? It is our custom at the clinic to make a plain roentgenogram of the urinary tract of every patient who has pyuria or a history of pyuria, irrespective of symptoms. This procedure should be more widely available and should be employed in routine diagnosis. Many clinicians seem to think

that a urinary calculus could hardly be present without a history of pain. It is surprising how often so-called silent or symptomless stones in the kidney, ureter, bladder or prostate gland are present, discovered in cases in which pyuria is the only clinical clue. There is nothing more embarrassing than to have the patient you treated unsuccessfully for pyuria consult another physician who finds urinary calculi. When shadows are found in the renal roentgenogram it should be remembered that calcified areas caused by renal tuberculosis also may cause shadows, which usually are recognizable in the roentgenogram.

The internist might also be justified in going a step farther by making an excretory urogram. This is a comparatively simple procedure, which often reveals lesions in the urinary tract that are least suspected. Although it may require wide experience correctly to interpret some of the excretory urograms, in many cases the nature of the lesion when visualized can be recognized by the inexpert practitioner. The value of excretory urography is not sufficiently appreciated by the average physician; it should be more generally employed in differential diagnosis. Not alone can it identify a renal shadow found in the plain roentgenogram, but it can reveal hydronephrosis and other lesions which are not suspected on the basis of the symptoms.

Having satisfied himself by these various means that the infection is an uncomplicated one, what is the internist's next procedure? The average physician of today probably would not hesitate to employ one of the sulfamido preparations against uncomplicated urinary infection and, in many cases, he would be rewarded by elimination of the pyuria after such therapy. What form of chemotherapy is it best to employ against urinary infection? As a general rule it is advisable, as far as possible, to use the drug which fits the bacteria present. If gram-negative bacilli are present, the choice lies between sulfamido drugs and preparations of mandelic acid. There is still a difference of opinion as to which drug is preferable. Most bacilli do not like an acid medium. In many cases of uncomplicated bacillary infection a combination of ammonium chloride or nitrate with mandelic acid, which lowers the hydrogen ion concentration of the urine to 5.3 or less, will eliminate the infection in six or eight days. This drug is even more efficacious than sulfamido drugs in combating infection caused by the *Streptococcus faecalis*. The *Proteus vulgaris* may offer difficulties if the hydrogen ion concentration of the urine cannot be reduced by means of acidification. In fact, when the urine remains very alkaline, no form of chemotherapy may avail. Unfortunately, patients of advanced years or those who have reduced renal function do not tolerate preparations of mandelic acid well. It is also true that some patients cannot tolerate sulfamido drugs, and for many of these the mandelate preparations will serve admirably. It must be said, however, that it is truly astounding to observe how bacillary infections will be eliminated by means of the sulfamido drugs. Against coccic infections

preparations of mandelic acid are of no value and when they are present the sulfamido group of drugs is preferable.

What particular sulfamido drug is most efficacious in the treatment of urinary infection? The list from which a choice can be made is truly imposing. It would seem, on the basis of experience, that those drugs most recently proposed, namely, sulfathiazole and sulfadiazine, have the advantage of causing fewer toxic reactions than do others and of possessing low acetylation and rapid excretion. There are those who prefer the sodium sulfa preparations. Sulfacetimide is another recent sulfamido drug which is extolled by some. Sulfaguanidine, which can be administered in the largest dosages without causing subjective reactions, is less effective than the others, although occasionally it is very bactericidal. There are several others; in fact, it might be claimed that this list is not up-to-date. It is hardly necessary to warn you against the danger of a patient's idiosyncrasy and variability in reaction to sulfamido drugs. It should be remembered also that if the infection does not respond to one sulfamido drug, another should be used. I have often observed that urinary infection which was resistant to one form of sulfamido drugs rapidly disappeared when another sulfamido drug or a preparation of mandelic acid was tried. Another observation should be made: it is seldom that sulfamido drugs interfere with the coincident administration of other drugs.

The subject of the dosage of the sulfamido drugs now arises. The internist is accustomed to dealing in large figures in the employment of sulfamido drugs, and he might look askance at the economical dosage employed by urologists. Experience has shown that an initial daily dosage of 3 or 4 gm. is all that is necessary against most uncomplicated infections in the urinary tract. In fact, the effective dosage is gradually being reduced and in most cases an initial two-day dosage of 3 gm. is being replaced by one of 2 gm., administered for a period of six or eight days. When such a low dosage is employed severe reactions to sulfamido drugs described by those who employ them in treating profound systemic infections are seldom seen. Urologists have the advantage that the infected field is immersed in sulfamide-bearing fluid, as is also the surrounding zone of reaction in the tissues, although the latter is the predominating factor. In contrast to the procedure in the treatment of systemic infection with a sulfamido drug, it seldom is necessary to determine the concentration of the drug in the blood in treating urinary infection, since this concentration is low and does not exert much influence so far as results are concerned.

Although this may not be the place in which to discuss toxic reactions in the use of sulfamido drugs, there is one complication not infrequently observed which deserves consideration and that is anuria developing as the result of acetylation and the deposition of crystals in the renal tubules. Although there is a difference in the degree of acetylation caused by the various sulfamido drugs, they all may be guilty of renal blockage. The degree of subjective toxic reaction which results is no criterion. The drug which

causes the least symptomatic reaction is one of the worst offenders in this respect. I refer to sulfadiazine. Sulfadiazine should not be regarded as being entirely innocuous, in spite of what Paul de Kruif has written in the *Reader's Digest*. Only the other day a report came from Bellevue Hospital in which it was disclosed that 10 patients had anuria after the use of sulfadiazine, with two deaths, in spite of treatment. One of these two deaths occurred after the administration of only 12 gm. of the drug in four days, or a dosage of 3 gm. daily. It should be emphasized that anuria associated with the use of sulfadiazine demands the immediate coöperation of the urologist. By the introduction of ureteral catheters and lavage of the ureters and the renal pelves, the blockage usually can be relieved. It is obviously advisable to start such treatment in the early stages of anuria. Crystallization otherwise may become so dense that lavage is futile and injury to the renal cells may be fatal.

In case pyuria persists in spite of a thorough trial of chemotherapy, what are the possible causes of failure of such therapy? A common cause is inadequate and incorrectly selected chemotherapy. This usually is the result of (1) failure to identify the bacteria present, (2) failure to recognize the existence of a mixed infection, (3) failure to select the correct drug for the particular bacteria involved, and (4) the occurrence of a toxic reaction. Probably the most important factor in the failure of chemotherapy is the existence of a primary lesion in the urinary tract which is the cause of pyuria; if such a lesion is not eliminated, chemotherapy of course is worthless. The list of such lesions is long, and even a brief discussion of them would lead far afield. Among them, however, those most commonly observed are chronic pyelonephritis with diffuse cicatricial changes in the renal tissues, inadequate drainage involving either the renal pelvis or the bladder, urinary calculi and tuberculosis. Needless to say, recognition and treatment of these lesions demand the knowledge and skill of the urologist. It is here that the urologic west begins, so to speak, with its wide horizons and unlimited possibilities, and it is here that my discussion will cease.

Summary

In summary these data may be repeated: Pus cells found in the voided urine of the female patient are of little or no clinical significance. In such instances a specimen of urine obtained by catheter is necessary. Pus cells in the voided urine of the male patient are of greater clinical value, and particularly if the two-glass test is employed. It is of equal clinical importance to determine the presence and kind of bacteria in the urine. Intelligent treatment of pyuria is dependent on a knowledge of its bacteriologic aspects. Rough identification of the type of organisms present is possible by the simple method of Gram's staining of the urinary sediment.

Bacillary infection is observed in most cases. The colon bacilli or the *Aerobacter aerogenes* are the organisms usually found. Mixed infection

may be present: most often it is caused by colon bacilli with *Streptococcus faecalis*. Unless this fact is recognized, chemotherapy may fail. Renal tuberculosis is a frequent cause of pyuria which resists chemotherapy. In recent years the symptoms and severity of the infection caused by renal tuberculosis have become milder and the recognition of such tuberculosis often is difficult. Auramine as a stain for the *Mycobacterium tuberculosis* is of greater value than carbolfuchsin.

Pyuria may be coincident with lesions situated in other organs. Acute cholecystitis coincident with pyuria often is observed. When a lesion requiring surgical attention is present, the question might arise, would urinary infection interfere with operation? As a rule it does not, but a search should be made for the cause of the pyuria. A careful search for foci of infection and the removal of them is always necessary. Pyuria or a history of previous urinary infection occurring with hypertension should be the guide to complete urologic investigation. In the presence of pyuria important clinical data can be obtained by such simple tests as the making of roentgenograms and excretory urograms.

Intelligent chemotherapy depends on identification of the bacteria. In cases in which the situation is complicated, infection caused by the *Escherichia coli* often responds to treatment with mandelic acid. Of the sulfonamides, sulfathiazole and sulfadiazine probably are preferable. The danger of acetylation with the deposition of crystals and the occurrence of anuria must be considered. Immediate catheterization of the ureters and pelvic lavage are indicated.

Persistent pyuria in spite of chemotherapy usually is caused by some underlying pathologic lesion in the urinary tract which requires careful examination and treatment by the urologist.

A HIGH FLUID INTAKE IN THE MANAGEMENT OF EDEMA, ESPECIALLY CARDIAC EDEMA

I. THE DETAILS AND BASIS OF THE RÉGIME*

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THIS paper presents the details of a régime which, in the past eight years, has been used in approximately 600 separate periods of treatment carried out on a series of about 400 cases of advanced disease, 96 per cent of which were cases of cardiovascular-renal disease. In this series there were about 375 cases, or 94 per cent, with gross heart disease, of which over 200 showed gross edema.

Only a few of the reasons which led to a trial of this régime can be mentioned here. There are clinical observations [77 to 93] from Withering through Austin Flint to recent times which are not discouraging to such a trial, and many facts are to be found in clinical investigations [23 to 76] of the last 15 years which appear not only to weaken the force of the usual objections to a high fluid régime, but also to explain the paradox of its good results. The 50 year old practice of the restriction of fluids in edema [87] appears incompatible with principles derived from renal-function and water-balance studies.[1 to 21]

The chief reasons urging a trial of this régime, however, were found in personal observations † at the bedside, such as:

1. The unmistakable clinical signs and symptoms of severe dehydration in some cardiac patients with massive anasarca.

2. The toleration by enlarged and fibrillating hearts in thyrotoxicosis of large amounts of water by mouth and by vein before and after operation.

3. Recoveries from so-called "postoperative nephritis," with correction of anuria and clearing of edema, by the administration of 6,000 to 7,000 c.c. of water for several days, mainly isotonic solution by vein.

4. The clearing of massive edema without disaster in cases of advanced nephritis, which often showed choked discs or grossly diseased hearts, in the face of intakes averaging more than 4,000 c.c. daily.

GENERAL CONSIDERATIONS

The fundamental thesis on which the régime is based was quaintly expressed by Baynard [77] in 1722: "salts creep with the chyle into the blood and have no way out but by the urine." A painstaking correlation of facts found in the newer investigative studies of body fluids,[22 to 37] renal function, [1, 2, 3, 4, 5, 6, 7, 8, 9] and body-water-exchange [23, 24, 25, 26] appears to eliminate

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† From 1930 to 1933 while instructor in internal medicine in Ann Arbor where Newburgh's renal-function and water-balance work was being applied clinically to nephritis and being applied to surgical problems by Coller and Maddock.[1, 2, 3, 4, 5, 6, 7, 8, 10]

the discrepancies in the old idea that "salt retention" is the *primary* factor in the formation of edema. Changes in venous pressure[52, 53, 54] and especially plasma proteins[48] follow as often as they precede the development or clearing of edema. Starling,[22] himself, emphasized the probable *primary* rôle of salt retention in some forms of edema.

Regardless of how the edema is formed,[38 to 54] it appears reasonably well established that:

1. Edema fluid is a simple volume increase of the interstitial fluid. It can accumulate and exist only if its materials have been supplied and retained. For each two pounds of edema these materials consist of about 10 grams of an alkaline mixture of sodium salts (about 5 parts sodium chloride with 1 part sodium bicarbonate, yielding a pH of 7.4) and 1,000 c.c. of water as solvent for the salts.[26, 34, 35, 36, 37] The increased volume of interstitial fluid is subject to the same vicissitudes as the normal volume; thus chloride or sodium deficits may exist, or water alone may be given up for vaporization and the whole mass of "brine" become concentrated and a true cellular dehydration exist. True dehydration in these "brine-logged" patients is, therefore, no real paradox.[21]

2. The alkaline edema fluid remains inertly and indefinitely retained or "stored" in the internal environment unless the bicarbonate fraction of its sodium salts is used up by the ever-forming metabolic acids[35, 37] or by ingested acids. Acidification incites the kidneys to balance the threat to the hydrogen-ion concentration of the body fluids by elimination of neutral or acid sodium salts or, as often expressed, "acidification mobilizes the sodium."[3, 8] As the *sodium* leaves the body via the kidneys its *water of solution* is free either (1) to leave the body as urine water, giving weight loss with diuresis, or (2) to leave the body as water vapor, giving weight loss with no diuresis, or (3) to remain within the body to remedy body fluid concentration and cell dehydration, giving, by a shift of water to the cells[23, 24] a disappearance of edema with no weight loss and no diuresis.

The retention of alkaline and the elimination of acid salts is a physiologic process[35, 37] which keeps the internal environment constant in volume as well as composition. To maintain acid base equilibrium slight changes in volume of interstitial fluid occur constantly throughout the 24 hours. If continued indefinitely in the one direction a continuous augmentation of volume of interstitial fluid leads eventually to clinical edema. In the other direction, in the absence of adequate water for the regulatory function of the kidneys, the continuous elimination of salts at the expense of body water leads to cellular dehydration and body fluid concentration and, finally, when about 8 per cent of the body water is exhausted, to anuria, accumulation of acid salts, and acidosis.

3. The sodium leaves the body via the kidneys in solution as urine; water reaches the kidneys only after all other demands of the body for water are met[6, 11]; the amount of urine-water needed for the elimination of the so-

dium depends upon the functional capacity of the kidneys.[5] Therefore, sufficient water must be supplied to the body so that *enough* water will reach the kidneys for the elimination of the sodium. The kidneys as "ultimate guardians of the internal environment" [35] are capable, even when intrinsically diseased or their function extrinsically impaired, of regulating the volume and composition of the internal environment if they receive enough water.[5, 6] Thus they prevent acidosis by eliminating neutral or acid sodium salts if an excess of sodium is present, or if sodium is at a premium they discriminate, conserve sodium, and prevent acidosis by eliminating other salts.[34, 35, 37] They fail partially or completely in their rôle of guardian when an inadequate amount of water is available for their use.[5, 15]

It follows from the above that the aim of this régime is to:

1. Decrease the ingestion of the material essential to the formation of edema and to encourage the mobilization of sodium already retained, by giving a diet restricted in sodium and yielding a neutral or acid ash.
2. Increase and hasten the normal effect of the metabolic acids, by the administration of minimal amounts of acid drugs.
3. Facilitate elimination of the mobilized sodium via the kidneys and avoid the development of true cellular dehydration, by administering plain water in adequate amounts, i.e., adequate according to water balance principles.[6, 13]

The trial of a régime based on these considerations was begun in the fall of 1933. It soon became apparent that the régime permitted the administration of large amounts of water to very ill edematous patients with impunity and benefit and with results better than those obtained previously by restricting fluids, whether the primary disease was nephritis, cardiac disease, eclampsia,[75, 76] pernicious anemia, or some "idiopathic" syndrome.*

Details of the Régime

Eight years of experience have disclosed many points which have improved results and shown that good results depend on the care with which the following details are enforced. It is not sufficient and is often productive of disappointing results to write as orders, for example, merely: "Force fluids; low sodium diet."

Acid and Other Diuretic Medication. Strictly speaking, these are not needed in the régime. The physiologic process of metabolism yields sufficient acid to use up slowly the bicarbonate fraction of the stored sodium mixture and incite its elimination if adequate water is furnished and the ingestion of an excess of alkaline ash is stopped. Usually slowly, but often with surprising rapidity, edema disappears with simply the neutral diet and an abundance of water.

* Results in our series of 402 cases, 241 with gross edema were reported in brief in St. Paul on April 22, 1942 and will be presented in detail in Part II of this communication.

Practically, however, acid drugs are often used to speed the elimination of edema for psychological and economic reasons as well as reasons of comfort. They have the added practical advantage in both hospital and home management of protecting from errors or lapses in the diet.

We use only dilute hydrochloric acid or ammonium chloride because their ions are entirely familiar to the body. Theoretically, a pure acid should be most effective. We have found well diluted hydrochloric acid to be so, regardless of its presence or absence in the gastric secretions. It is obvious that large amounts of ammonium chloride unnecessarily increase the total solids which must be eliminated.

Mercurial diuretics are used infrequently to speed elimination when the degree of the edema is a major cause of discomfort. In only the most advanced and resistant cases is their use necessary in this régime. When they are used the water given is increased[91] to a maximum to avoid the post-diuretic dehydration and shock so often noted with restricted fluid régimes.[55, 56, 57, 58]

High protein diets,[9] acacia,[59, 60] thyroid extract, and vitamin B have not been used in order not to confuse results and to limit variables as much as possible.

Hypertonic solutions are not used.[62, 63] In our experience *no case* resistant to this régime (because of our inability to administer sufficient water to make it effective) has responded satisfactorily for any length of time to hypertonic solutions and restriction of fluids.

Administration of Acid Drugs. When no oral intake is possible we content ourselves with supplying water parenterally and depend on the constantly forming acids of metabolism to mobilize sodium. If response is slow, 1–2 c.c. of mercupurin is given after a day of good intake and the total intake increased afterwards to protect from post-diuretic dehydration.

If the patient is only able to take clear liquids, a few drops (2 to 5) of diluted hydrochloric acid in each glassful is often well tolerated and often serves to speed elimination.

When the oral intake is well established or the initial neutral diet is tolerated, 5 to 10 drops of diluted hydrochloric acid may be given in a full glass of water every hour from 7:00 a.m. to 7:00 p.m.; or it may be given 15 to 30 drops at each meal or feeding.

Ammonium chloride is given for reasons of convenience or if the acid is not tolerated; rarely in a greater amount than 15 grains four times daily (4 grams daily), and usually not more than 2 or 3 grams daily.

After dismissal only the more severe cases, or milder cases who neglect the diet grossly, need the acid medication. These rarely need more than 45 grains (3 grams) of ammonium chloride or 40 min. (2 to 3 c.c.) of diluted hydrochloric acid in the day.

Dietary Regulation of Sodium. Meticulous attention to diet is not necessary or logical if edema is mild and has no tendency to recur. However,

when massive edema is resistant to treatment or continually recurs, diet therapy is rewarded as richly as in cases of severe diabetes.

Too frequently we consider obstinate cases as terminal or not subject to further improvement because they respond no longer to frequent and heavy doses of mercury and acidifying drugs and strong hypertonic solutions. Many such cases will respond and remain evenly edema free on a neutral diet. All cases are easier to manage and require less mercury and acid. The diet in our experience is no more difficult to explain or to enforce than a diabetic or ulcer diet. Even the recalcitrant patient soon comes to prefer it to the disability and suffering of his edema and the expense and inconvenience of intravenous mercury and hospitalization.

The diet is not simply a low salt diet, nor is it merely a low sodium diet. At all times it must yield a neutral or slightly acid ash. This prevents the neutralization of the metabolic acids which mobilize already stored sodium, and prevents the retention or "storage" of what sodium is taken in the diet. Some of Schroeder's[93] cases show that edema does not clear on a diet in which salt is reduced to the very low figure of 0.5 gram, a figure at which the *reaction* is basic.

Construction of a diet to fulfill these requirements depends simply on our knowledge[8] that milk, all vegetables, and all fruits (except prunes, plums, and cranberries) yield an excess of alkaline ash. We must, therefore, not only restrict table salt and sodium salts but must insure the balancing, at each feeding, of the foods mentioned above with the foods that yield an excess of acid ash, which are meat, chicken, fish, eggs, cereal foods (including corn) and the three excepted fruits mentioned above. (Appendix: "Skeleton Outlines.")

The familiar Karrell diet, at the point where eggs, cereal and toast are added, if low in salt, can be just such a diet. In a patient strong enough to take food, starting such a diet is often followed by a prompt diuresis and loss of edema. This is not simply the result of sodium restriction and the supplying of acid; the non-liquid articles of the diet supply 700 to 1,200 c.c. of water for the use of the body.[6] A very ill patient who voluntarily drops to such a diet, or who works up to it, may lose edema quickly and be considered to have had a "spontaneous diuresis." The effectiveness of a high protein diet or a "dry" diet may well be due to the fact that such diets almost of necessity yield a marked excess of acid ash.

Either in hospital or at home one must guard against the ingestion of anything which renders useless the restriction of sodium or unbalances the acid-base proportion. A few glasses of milk or citrus fruit juice from the between-meal nourishment tray or a few doses of sodium bicarbonate for "gas" or indigestion may result in failure of the régime. Extra alkaline fruit juice or milk can be fairly well balanced by about 15 drops to the cup of diluted hydrochloric acid. If the primary disease requires the use of the sulfonamides or salicylates, it is essential to prescribe calcium carbonate to go with them instead of sodium bicarbonate, and to use acetylsalicylic

acid instead of sodium salicylate. Patients must be warned against commercial salt substitutes (mainly sodium salts of some acid), against "soda" and commercial alkalis for indigestion, and against forcing fluids with unlimited amounts of milk or alkaline fruit juices. Conversely, acid-base proportion may be unbalanced by failure of the patient to eat the acid-ash foods offered him in any one feeding. Every item of each meal or feeding should be eaten; but if anorexia or caprice results in the omission of acid-ash items, equivalent basic-ash items must be omitted. (See Appendix: "Precautions for Neutral Diets.")

The Diets. The diets used in the régime are based on the "neutral" diets and on the tables in Newburgh and MacKinnon's * *Practice of Dietetics.*[8]

The "Initial Neutral Diet" is appropriate as soon as soft food is tolerated. It yields only about 0.85 gram of sodium and an excess of acid ash amounting to about 100 c.c. of tenth normal hydrochloric acid. It is usually the first diet ordered in the hospital and it is very effective for home use when hospitalization has been refused or in the event of a minor recurrence of edema after discharge. (Appendix: "Initial Neutral Diet.")

As the ability to take food increases the Newburgh-MacKinnon tables permit the construction of liberal "full" neutral diets to fit any caloric requirement and any coincident disease such as diabetes or peptic ulcer or obesity. (Appendix: "Full Neutral Reduction Diet.")

At the time of discharge, if it appears that the neutral diet tables are likely to prove too difficult, a quite effective, simplified diet may be furnished. Strongly alkaline vegetables and fruits are forbidden entirely; milk, vegetables and fruits, with the exception of prunes, plums and cranberries, are specifically limited in amounts to insure a definite preponderance of acid ash. (Appendix: "Full Neutral Diet.")

After edema is gone and if for psychological reasons anorexia develops on account of the tastelessness of the food, a minimum of salt in the cooking combined with an increase in the acid ash of the diet will often be tolerated without recurrence of edema; within limits, *reaction* is more important than total sodium.

These diets are rich in milk, eggs, and fresh meat; and liver, yeast and wheat germ may be given in any amount. But if iron or vitamin deficiency is present or is feared, especially during the short period of the "initial" neutral diet, vitamin and iron supplements may be given.

The High Water Intake. In some moderately severe cases attention to the primary disease, the use of acids, and the regulation of sodium ingestion may either separately or in combination so lessen the body's needs for water that elimination of the edema occurs in spite of a restricted intake. However, even in these cases the liberal use of water does away with discomfort from thirst, makes the work of the kidneys easier and protects the cells from any degree of dehydration.

* Frances MacKinnon gave us helpful criticism of the Appendix diet lists.

In the most severe cases, however, very large amounts of water may be needed for water vapor and for urine water. Unless enough water is administered edema either does not clear at all; or it clears in part or even entirely but only at the cost of a degree of concentration of body fluids and of dehydration of the cells more harmful to the cells than the presence of edema.[55, 56, 57, 58, 59, 60, 61, 62, 63] In such cases, until advancing disease makes it no longer merciful or possible to administer large amounts of water, edema can be cleared, its recurrence prevented, and dehydration avoided only by an adequate increase in the amount of water administered.

Much of the satisfaction with the almost universal practice of severe restriction of fluids[37] appears to be due to the protection from disastrous cellular dehydration during the early days of edema loss by the release of edema water for vaporization purposes, the salts being eliminated in a fraction of the water which held them in solution in the body. Later, as the edema water is exhausted, protection from otherwise inevitable dehydration[57] is afforded by relaxation of the water restriction or by increased amounts of diet water derived from increasing ingestion of food.

The Amount and Kind of Water. Only renal-function and water-balance studies show us *how much* water is *enough*. In health about 1,200 c.c. are required for water of vaporization and stool, and 1,500 c.c. for a good margin of urinary water. In milder cases of edema we give a total of 2,500 to 3,000 c.c. of water as a minimum, leaving the water derived from the non-liquid portion of the diet (700 to 1,200 c.c.) as a safe margin.

Under certain circumstances, in severe illness, the needs of the body for water are greatly increased. Temperature regulation may use as water vapor 2,000 to 5,000 c.c. daily.[14] Badly impaired kidneys may require 2,000 c.c. or more daily to eliminate 40 grams of solids,[5] and when the maximum specific gravity is low we increase the intake by 1,000 to 2,000 c.c. over the usual amount. Dehydration may have resulted in a loss of body water, not electrolyte, that amounts to from 6 to 8 per cent of the body weight[6, 11]; such a water deficit, of from 4,500 to 6,000 c.c., must often be made up during the first few days before any useful amount of water reaches the kidneys.[11] Thus, a badly dehydrated, edematous patient with badly impaired kidneys and with a fever or much sweating, might require 8,000 to 10,000 c.c. of water for a day or two, and 4,000 to 5,000 c.c. daily thereafter.[6, 13, 14]

Less than enough water for the needs of the body leads eventually to dehydration. *Any reasonable amount* more than enough does no harm because plain, unloaded water passes out via the kidneys[22] rapidly and easily even when their function is badly impaired.[5] Within a wide degree therefore, as Austin Flint[31] said, *more than enough* water is not *too much*. We have never encountered "water-intoxication" and suspect that these syndromes are due to disturbances of the electrolyte pattern.[32, 33, 19]

The best kind of fluid to use is indicated by Baynard (1722) who says "*that* water is the best, which is most simple as having least contents."

Water is needed, not the solid content of fluids. Oral fluids should not carry large amounts of alkaline ash or salt, as do citrus fruit juices and salted broth. Parenteral fluids should carry no salt and a minimum of solute.

No normal saline is given unless the plasma chlorides are very low or there are marked clinical signs of hypochloremia or unless the carbon dioxide combining power is very low.[19] We have repeatedly observed that when enough water is reaching the kidneys they are capable of conserving enough of the excess sodium or chloride of the edema fluid to rectify the electrolyte pattern, even while the water of the edema fluid is being rapidly eliminated.

Isotonic dextrose, 5 per cent in distilled water, is used because most of the solute is oxidized or stored in the cells. It is *the solution* which yields a maximum of plain water for the use of the body. In two instances we observed no untoward effects from the accidental administration of 1,000 c.c. of plain distilled water in about an hour. We commonly rehydrate our patients with diabetic coma with two-thirds normal solution.

Administration of Water. It requires patience and some ingenuity to administer large amounts of water to the very ill. When nausea and vomiting or stupor are present, or for other reasons an adequate amount of water cannot be given orally, enough intravenous solution is given to bring the total intake up to the estimated desirable amount. Rectal administration of water is satisfactory only in the first few hours when general dehydration is marked; expelled enemas upset intake figures and may result in abnormal electrolyte losses.

Since the first trials of 300 to 500 c.c. of 10 per cent dextrose in 1933 the amounts administered have been increased. At present 500 c.c. or 1,000 c.c. of 5 per cent dextrose in distilled water are given from one to six times a day. On occasion 1,500 to 2,000 c.c. have been given continuously, without untoward effects, in from 60 to 100 minutes.

The only untoward reaction encountered (in only 20 of about 2,000 administrations) with the use of isotonic solutions that carry no diuretic, which justifies stopping the intravenous injections, was an increasing "sense of fullness"; the symptom appears related to effects of the electrolyte of the solution rather than to its rate or volume. We suspect that many of the reported reactions are post-hoc affairs, episodes of the disease under treatment occurring naturally, or precipitated by fatigue and annoyance from slow-rate venoclyses.[29, 30, 31, 63]

The most desperately ill cases have almost invariably shown evidences of severe dehydration associated with their massive edema.[88, 89, 90, 91] The water of the first few intravenous injections is used to bring all of the body fluids up to a normal dilution and to relieve the water deficit of the cells.[11] During this period there is, quite naturally, often no diuresis, some gain in weight, and sometimes a visible increase in the edema. Coincidentally, there is usually such marked clinical improvement as to encourage one to persist. Persistence is usually rewarded, often in some very unpromising cases, by a diuresis and the clearing of edema.

When the oral route becomes possible, a tedious insistence is often necessary to bring the oral intake up to the point where it is wise to discontinue intravenous supplements. If the intake is poor on account of continuous semistupor, Austin Flint's practice[82] of administering small amounts of water frequently through the night as well as through the day may be effective. When liquids can, at last, be taken freely it is important to recall the necessity of avoiding large amounts of alkaline-ash fruit juices, salted broth and milk.

As general improvement continues it is usually surprisingly easy to keep the intake at any level desired. Not infrequently, however, one encounters the patient whose oral intake is inadequate simply because of forgetfulness, obstinacy, or a life-long aversion to water. We have found it very effective to prescribe something in "homeopathic" doses to be taken in a glass of water every hour, or even every half-hour, from morning until about six at night. We use a few drops of hydrochloric acid, peppermint water, or a half a teaspoonful of wine (vide Galen's wine water[77]).

Such efforts to increase oral intake so that intravenous supplements may be stopped are justified because all patients "do better" on an oral intake with even scanty liquid nourishment.

Comment

In any trial of the régime the details and precautions outlined above should be strictly followed. It would be wise to proceed at first as we did, making the trial on quite mild cases or on cases that have obviously failed to respond to accepted régimes, especially until the dietitians and nursing staff are reasonably familiar with the régime. (Appendix: "Sample Hospital Orders.")

Because we undertook these observations as a practical clinical investigation we often carried our intakes higher than optimum. As a consequence, we have repeatedly observed the rapid clearing of massive edema in the face of intakes averaging 6,000 or 7,000 or even 8,000 c.c. daily, in spite of the presence in some instances of pulmonary edema, choked discs, or convulsions at the time of admission.*

In our hands this régime has proved effective in eliminating edema and preventing its recurrence in the most resistant type of case if, and so long as, it has been possible to administer adequate amounts of water. The type

* These phenomena appear to bear no direct relationship to anasarca and occur frequently in its absence. Pulmonary edema, for example, appears to be most directly related to an injury of the cells of the capillaries by a lack of oxygen or by a lack of cell water. The "brinelogged" patient may need plain water to relieve severe cellular dehydration.[49, 50, 51, 55, 56, 57, 67]

In connection with the high intakes it is reassuring to recall some approximate figures and certain facts. An oral intake of 8,000 c.c. adds only 16 pounds to the four tons moved by the heart in half a day. One liter by vein moves along through the heart with 150 to 300 liters in an hour. The circulation is protected from "over-burdening" by rapid vasomotor adjustment of volume, and by rapid elimination of plain water (1000 c.c. or more, in an hour) through even impaired kidneys. If these fail, protection is afforded by quick escape of fluid through the 68,000 sq. ft. of capillary bed which shows a sieve-like permeability to the small molecule electrolytes and water of isotonic saline or isotonic glucose solutions.[22, 34, 37, 44]

of terminal case which has not responded to this régime does not respond to the usual régimes which restrict fluids and use strong hypertonic solutions or acacia. On the other hand, many cases of massive edema which had resisted well carried-out restricted fluid régimes have been observed to respond to this high fluid régime.

Summary

1. A régime is presented which permits the effective management of edema with a high fluid intake by the proper regulation of sodium ingestion.

2. The régime is based on renal-function and water-balance principles which the accepted practice of the restriction of fluids appears to ignore.

3. The reasons for a trial of the régime are briefly indicated.

4. The details of the régime, some diet lists, and certain precautions are presented as they were evolved from eight years' experience with 626 separate periods of treatment of 402 cases.

APPENDIX

Diets and Orders

Skeleton Outline for Neutral Diets *

General Diet

Limited 24 hr. Maximum	Basic-Ash Foods	vs.	Acid-Ash Foods	No Limit 24 hr. Minimum
1 Pint	Milk		Eggs	2
2 Servings	Vegetables		Meat, fish, fowl	1 Serving
2 Servings	Fruits		Bread or cereals	5 Slices or servings
		except:	Prune, plum, cranberry	as desired

Initial Diet

6 Cups	Six small feedings		One item per cup
6 Servings	Milk or	Egg or	1
	Milk and	Bread or	2 Slices
	Cream (1/3)	Cereal	1 Cup

Precautions

1. No salt or soda in or on food.
2. No prepared foods containing salt.
3. No salted broth or extra juices or extra milk.
4. No "vegetable" salt, no soda for "gas."

* A "neutral" diet is not a low-salt, or low-sodium, or acid-ash diet, but a combination of all three; and the diet reaction is, within limits, more important relatively than the total sodium or salt. Therefore each meal or feeding is balanced, and if any acid-ash item is not eaten an equivalent basic-ash item must be omitted. The diets are based on the Newburgh-MacKinnon tables.[8]

Initial Neutral Diet

Six Small Feedings, with Protein 60–70, Calories 2400

Food	Wt.	Measure	Food	Wt.	Measure
	gm.			gm.	
1. *Cereal and Cream*			2. *Eggnog*		
Cereal prepared	15	¾ cup	One egg	—	—
or uncooked	15	1 tbsp.	Milk	100	½ cup
or cooked	100	½ cup	Cream 20%	100	½ cup
Cream 20%	100	½ cup	Sugar and spice	—	—
Sugar	10	2 tbsp.			
3. *Fruit, Bread and Milk*			4. *Corn Soup*		
Prunes	100	½ cup	Corn puree	70	⅓ cup
Bread	30	1 slice	Bread	30	1 slice
Butter	10	1 pat	Butter	10	1 pat
Milk	200	1 cup	Cream	70	⅓ cup
5. *Eggs, Toast and Milk*			6. *Bread and Milk*		
One egg	—	—	Milk	200	1 cup
Bread	30	1 slice	Cream 20%	30	1 tbsp.
Butter	10	1 pat	Bread	60	2 slices
Milk	200	1 cup	Butter	15	1 tbsp.
Cream	30	2 tbsp.			

Notes: Whole wheat bread prepared without salt; butter to be unsalted or washed.
Cereal prepared without salt; farina, cornmeal, cracked or ground whole wheat, oatmeal, puffed rice or puffed wheat only.

Any one feeding may be repeated or substituted for another, but the two eggs and the milk for the day must be taken. Extra bread, cereal and eggs may be taken if patient is not overweight.

When digestion is weakest prunes should be souffled and the corn soup feeding replaced by feeding 6.

When digestion is stronger plums and cranberries may be used in addition to prunes; and chicken, fresh fish or lamb substituted for the egg in 5.

Additional Liquids: Weak tea or coffee with sugar; unsalted weak chicken or beef broth. Prunes, plum and cranberry juices well diluted in water (1:4). Water flavored with fruit flavoring (Kool-Aid, etc.).

Desserts: Clear jello, wine jelly, angel food or sunshine cakes; as desired.

Precautions for Home Use

1. *No food or drink other than above. All* of each feeding must be eaten.
2. *No salt substitutes* except the Ammonium Chloride furnished you.
3. *No soda or alkali medicines* for "gas" or indigestion other than the Calcium Carbonate furnished you.
4. Measure out three quarts of water and take by 7:00 p.m.
5. Take two to five drops of the liquid medicine furnished you in a glass of water every hour until 7:00 p.m.

FULL NEUTRAL DIET

(Low-Sodium, Acid-Ash, Calories Unrestricted)

Foods Unrestricted as to Amount (from which *at least* two or three servings must be taken for any one meal):

Eggs: Two equal one serving (which can be substituted for a meat serving).
Meats: Meat, fish or chicken; one serving of about ¼ lb. a day.
Bread: Plain breads without nuts or raisins. Whole wheat bread preferable (five slices, or cereal food servings as substitutes, in each day).

Cereal: These only (one serving a day at least)—oatmeal, farina, quick-cooking cream of wheat, cracked or ground whole wheat, corn-meal mush, hominy, puffed rice or puffed wheat, "muffetts."
Cereal Foods: Servings may be taken at any meal and must be taken if meat or egg is not eaten: macaroni, spaghetti, rice, home-made noodles, corn.
Fruit: Prunes, plums and cranberries. For other fruits, see below.

Foods Restricted as to Amounts (from which *no more than two* servings should be taken for any one meal):

Vegetables: Two servings a day of ½ cup each of any vegetable except parsnips, lima beans, rhubarb, chard and spinach, which are forbidden. One small potato equals a serving. Use fresh or frozen vegetables or those canned without salt.
Fruit: One serving of ½ cup of fruit or fruit juice daily except raisins and dates which are forbidden.
Salads of fruit or vegetable may be made from the above, as desired.
Raw fruit and raw vegetable should be used several times a week.
Milk and Milk Products: Two cups of milk daily, including that used in preparing food. *Cream:* two tbsp. in coffee or tea, ¼ cup for breakfast cereal. *Ice Cream:* Without fruit or nuts, one small scoop in a day. *Cheese:* Only unsalted, cottage cheese (which may be substituted for a meat or egg serving).

Other Foods and Food Combinations:

Soups: May combine vegetables, as allowed above, with milk allowance or with salt-free broth to make soups. Salt-free clear beef or chicken broth may be taken as desired both with and between meals.
Desserts: No limits as to amount: Plain jello, wine jelly, plain tapioca, angel food or sunshine cake. (No cake or cookies made with salt, soda or baking powder.)
Limited by milk allowance above: Custard, junket, cornstarch pudding, egg-nogs, ice-cream. Fruit as indicated above.
Beverages: One cup of tea or coffee to each meal, chocolate made with milk allowance. (See Precautions for Neutral Diets.)
Neutral Foods: Which may be taken in any quantity desired: Sugar, butter, oil, gelatin, salt-free salad dressing, plain tapioca and plain cornstarch, clear sugar candies.

Sample Menu

Breakfast:	*Lunch:*	*Supper:*
½ cup orange juice	Corn soup	Roast beef
1 soft boiled egg	1 poached egg	1 small baked potato
and/or cereal	on toast or	½ cup asparagus
¼ cup cream	Buttered noodles	Bread
Toast, 1–2 slices	Lettuce salad	Coffee
Coffee.	Bread	½ cup plums.
	Milk, 1 cup	
	½ cup baked custard.	

PRECAUTIONS FOR "NEUTRAL" DIETS

1. No salt or soda to be used in the cooking or at the table.
   Small amounts of ammonium chloride may be used as a salt substitute.
   Use no other salt substitute, such as "vegetable" salts (Eka, etc.).
2. Obtain unsalted sweet butter or wash butter free from salt.
   Obtain unsalted bread from baker, or make at home.
   Unsalted salad dressing must be made at home.
3. *Take no* salted appetizers or salted foods such as salted nuts, potato chips, sardines, olives, pickles, relishes; no cheese except unsalted cottage cheese; no smoked or salted meats or fish such as canned salmon or tuna, bacon (unless par-boiled), ham, lunch meats, sausage, salt pork.
4. *For "gas" or "indigestion":*
   Take no bicarbonate of soda and no alkali powders or tablets (Tums, etc., etc.).
   Use calcium carbonate only.
   Avoid cabbage family, turnips, rutabagas, peppers, radishes, onions, spices, greasy fried foods and pork.

5. *For extra liquids:*
   Take none of the vegetable juices or fruit juices on the restricted list, or milk or salted bouillon.
   Use only well diluted plum, prune or cranberry juice, or water with fruit flavoring (such as Kool-Aid) or unsalted chicken or beef broth.

FULL NEUTRAL REDUCTION DIET

(1,000 Calorie)

Food *	Amounts	Sample Menu
	Breakfast	
Fruit	See list	Orange juice
Cereal (skimmed milk)	½ cup	
or		
Toast	1 slice	Toast
Egg	1	Egg
Butter	½ teaspoon	Butter
	Lunch	
Eggs or	2	
Lean meat, fish or chicken	1 serving (2 oz.)	Sliced chicken
Vegetable	See list	Tomatoes and lettuce
Bread	1 slice	Bread
Butter	½ teaspoon	Butter
Milk (skimmed)	½ glass	Milk
	Supper	
Fish, lean beef, chicken, lamb, veal, or mutton	1 serving (3 oz.)	Roast beef
Vegetables	See list	Peas
Fruit	See list	Plums
Milk (skimmed)	½ glass	Milk
Bread	1 slice	Bread
Butter	½ teaspoon	Butter

* *Notes on the FOOD:*
Fruits: Prunes, plums or cranberries must be used for one of the two fruit servings.
Cereal: Use only oatmeal, farina, ground whole wheat, puffed rice or puffed wheat.
Bread: Whole wheat bread preferably. (May use as substitute for one slice of bread: ½ cup of rice, macaroni, noodles or spaghetti.)
Tea and Coffee: Clear or with saccharine as desired.

List of Vegetables and Fruits: Only these, in the amounts shown, are permitted.

One-Half Cup Amounts			Other Quantities	
Endive	Lettuce	Green pepper	Cabbage family	⅔ cup
Radish	Squash	Egg plant	Tomatoes	⅔ cup
Watercress	Turnips	Mushrooms	Tomato juice	½ cup
Onion	Peas		Asparagus	1 cup
Pumpkins	String beans		Corn	⅓ cup
Lemon juice		Peach	Grape juice	⅓ cup
Grapefruit, or its juice		Grapes	Fresh prune	⅓ cup
Orange, or its juice		Apple	Melon	⅔ cup
Raspberry		Strawberries	Pineapple	1 slice
Pears		Apricots	Banana	½
Blueberries				

(Fruits should be fresh or canned, or cooked without sugar.)
(Vegetables should be fresh, frozen or canned without salt.)

Notes on the Weight Reduction

1. Do not eat anything not on the diet. Eat *all* of each meal.
   Do not add butter or cream sauces to the food.
   Do not drink soft drinks, alcoholic drinks or extra fruit juices.
2. Water is not fattening, drink 8 to 12 glasses daily.
3. When tired or weak, *rest, do not eat.* Clear tea or unsalted broth is permitted and is refreshing.

"Precautions for Neutral Diets" must be appended here as on the "Full Neutral Diet" above.

(This "neutral" diet has been useful in cases of simple obesity which are not losing weight properly due to "water retention," i.e., sodium retention.)

SAMPLE HOSPITAL ORDERS

A. For massive anasarca with no great mechanical embarrassment from the edema and no great trouble in eating or drinking:

Orders: 1. Initial neutral diet.
2. Intake to 4,000 c.c. daily.
3. Diluted HCl M. 5 in a glassful of water every hour until 7:00 p.m.
4. Ammonium chloride gr. viiss (enteric coated) 1 tablet t.i.d.
(or 1 tablet after each of the six feedings).
(5) If needed to bring intake to 4,000 c.c., 500–1,000 c.c. of 5 per cent glucose in distilled water i. v.

B. For massive anasarca with marked embarrassment from the edema and with inability to take significant amounts of liquids:

Orders: 1. Water orally as tolerated with 2 drops of diluted HCl to each glass.
2. 500 to 1,000 c.c. 5 per cent glucose in water i.v. at 7 a.m., 1 p.m., and 7 p.m.
3. Mercupurin 1 c.c. i.v. second hospital day.
(4) Begin orders under A. as soon as possible.

It is assumed that appropriate methods for the treatment of the primary disease and its symptoms are in force. Total intake and output are routinely recorded for 24 hour periods terminating just before breakfast, at which time the patient is weighed daily when possible.

Only when the dietitian and the nursing force are familiar with the details of the régime and the precautions to be exercised, will simple orders such as those above be sufficient to put the régime into effect.

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ORIENTATION OF TREATMENT IN THROMBOPHLEBITIS, PHLEBOTHROMBOSIS AND PULMONARY EMBOLISM *

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THE treatment of venous thrombosis is very much a method of "damned if you do, damned if you don't." One is never quite sure which case may develop a fatal pulmonary embolism. Out of the welter of confusion on this subject, however, are evolving certain principles which seem reasonable but which may need revision in the future.

In the first place, there are now four new well accepted therapeutic procedures, venous ligation and section, paralumbar sympathetic procaine block, anticoagulant therapy and sulfonamide drugs. I shall attempt to point out in what type of venous thrombosis each method seems most applicable.

One may quote statistics pointing out that most patients with fatal pulmonary embolism die without warning and without premortem evidence of any phlebitis in the extremities where it might be detected and the physician be forewarned. This is true to a degree, but I am convinced that a greater degree of consciousness of this possible eventuality would lead one to discover warning signs. Again and again after a benign pulmonary embolism or thrombophlebitis of a leg vein has become apparent, questioning will bring forth the reply from the patient, "Oh yes, I had a little pain in my calf yesterday but thought it was stiffness from lying in bed." Or review of the temperature chart brings forth the fact that the patient had run an unexplained, low grade septic fever two to three days before the embolism occurred. Therefore all fat patients, patients with sluggish circulations, or above all with histories of previous thrombophlebitis following childbirth or surgery, upon whom have been performed cholecystectomies, herniotomies, hysterectomies, Mikulicz operations, colectomies, or Miles resections, should be routinely examined for a positive Homans' sign, pain in the calf, swelling of the legs, and low unexplained septic fever, especially during the critical eighth to sixteenth postoperative days.

A properly conducted dawn patrol will prevent a Pearl Harbor and prophylaxis is the best cure. Of all measures I believe bicycle exercises faithfully supervised by the nursing staff are the most effective. The past winter (and why do these epidemics of pulmonary embolism come in winter time?) there were four patients with pulmonary emboli and two with thrombophlebitis, a total of six cases, in one of our hospitals, contrasted with 14 patients with venous thrombosis with or without pulmonary emboli in another hospital, the latter hospital having by actual count a surgical service

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only 10 per cent more active. In the first of these hospitals, bicycle exercises were most assiduously supervised by the nursing staff, but in four cases in which thrombophlebitic complications occurred these exercises had been deferred, because of a vulvectomy in one, and because of clamps to the bowel in the three others. We are now changing our routine to a gentle range of bicycle motion in such cases not believing the danger to clamps to be as great as that from stagnant circulation in veins. For cases suspected of developing thrombophlebitis we include in our routine ace bandages to the legs, a cradle of lamps, and avoidance of flexing the thighs on the abdomen. It is well worth while to go down the ward pulling pillows out from under the knees of patients. Reduction of weight before performing operations of choice is a very valuable procedure.

These constitute our measures to prevent sudden death by pulmonary embolism which may occur without any warning. Such emboli metastasize from pelvic veins or from leg veins at the moment of their formation before local signs have developed. One other prophylactic measure is to be mentioned: mass anticoagulant therapy of our surgical hospital population, first by heparin which is far too expensive; and second by dicoumarin, which is still experimental, and which in my hands has proved too erratic and too dangerous. In 25 cases I have had one death, one barely saved from death by repeated transfusions, and two other minor hemorrhages (hematuria and gluteal hematoma). The doses used in these patients who suffered hemorrhages were no greater and were often less than in the patients who failed to respond with prolongation of coagulation time. An intravenous salt of dicoumarin given once in 24 or 48 hours may prove more reliable by avoiding the element of variability in absorption.

We now come to the question, what shall be done for the patient who has obvious phlebothrombosis or thrombophlebitis, or the patient who has already had a warning benign pulmonary embolism of unknown source or from a pelvic venous thrombosis. Here the "damned if you do and damned if you don't" comes in.

There are five methods of treatment available, one old—heat, elevation, immobility of an involved limb and rest; three new—(1) ligation and section, (2) paralumbar sympathetic procaine block, (3) anticoagulant therapy with heparin, dicoumarin or a combination of both, and (5) sulfonamide drugs. The value of these procedures cannot be determined until mass statistics are available, and I have none. However, certain experiences stand out in my mind. I have seen a patient after two courses each of 10 days of heparinization die of pulmonary embolism one hour and 25 minutes after stopping the heparin because the femoral vein was not ligated when he had two warning benign pulmonary emboli. I have seen another die of progressive clotting in the pelvic veins extending up into the inferior vena cava after ligation of the femoral vein following a warning benign pulmonary embolism, and this progression occurred because anticoagulant therapy had not been used. I have seen a patient return with a badly swollen leg which

had not swollen in the hospital during bed rest and heparin therapy, and this swelling probably could have been prevented by paralumbar sympathetic procaine block. In this patient, belated block fortunately greatly alleviated pain and swelling, as I have sometimes seen it do even 19 months after the original thrombophlebitis.

Venous thrombosis falls into six classifications, and each type is fraught with different dangers as regards likelihood of pulmonary embolism. Here we deal with the problem of the clinician facing a recognizable, developed lesion and wondering what to do in order to prevent a pulmonary embolism from occurring or recurring as the case may be.

1. Phlebothrombosis (Ochsner). This type, occurring in the calf veins, often with no swelling and only slight or no fever, with soreness in the calf and pain in the upper calf on flexing the foot as in eliciting an ankle clonus (Homans' sign), often first gives evidence of its presence by pulmonary embolism. Tenderness may already be present or soon appear in the saphenous triangle. This type is common following abdominal or pelvic surgery and is dangerous as regards pulmonary embolism. If the patient is over 50 and a warning embolism has occurred, I believe this is the prime indication for ligation and section of the femoral vein. Administration of heparin should be immediately instituted after ligation and section because other veins may already be involved or become involved and emboli be cast off from them. Indeed, it is quite probable that a second embolism in such cases probably comes more often from a second focus of venous thrombosis than from the already organized clot in the recognized focus. This thought leads some to cast doubt on the necessity of ligation of the femoral vein. However, experience with a patient who had multiple pulmonary infarcts at first diagnosed as coronary occlusion and who ceased having such accidents after ligation and section of a thrombosed femoral vein, and another patient who at postmortem examination showed the only possible source of his infarct to be the original thrombus in the femoral system have confirmed to me the value of this procedure.

2. Venous Thrombosis of the Pelvic Veins. This location seems to me the most dangerous source of pulmonary emboli by a ratio of about 3:1 in comparison to leg veins. Here there may have been only two to three days of a warning low septic fever and then a benign pulmonary infarct occurs. The best treatment is by anticoagulants. We have now successfully treated 11 of these patients by combined heparin and dicoumarin (none of the accidents quoted above occurred in this group of cases with combined therapy). The heparin is given for immediate effect, and the dicoumarin takes over after a latent period of two to five days when the tedious and expensive continuous administration of heparin intravenously may be discontinued. The moment of dicoumarin effect is judged by a falling prothrombin percentage. It is understood that an anticoagulant does not prevent an embolus from being cast off from a venous thrombus already formed, but it will prevent further thrombus formation, more dangerous as regards

embolism than the older recognized thrombus, and it will prevent propagation of an embolus in the pulmonary arteries.

3. Thrombophlebitis of the Femoral System. (Phlegmasia alba dolens or "milk-leg.") This is an inflammatory process involving the whole sheath including the arterial sheath and perivascular network. The thrombus is tough and adherent, and emboli rarely occur except sometimes very early in the process before the leg is recognized as a "milk-leg." Hence ligation and section are not necessary in this lesion. The prime indication is paralumbar sympathetic procaine block with simultaneous anticoagulant therapy. The block is to be regarded as symptomatic treatment, abolishing reflex arterial spasm, thereby increasing arterial circulation which in turn enhances lymph circulation, reduces swelling, abolishes pain, and greatly shortens convalescence. The anticoagulant therapy prevents extension into the pelvic veins and propagation of the same process in the opposite leg.

4. Superficial thrombophlebitis migrans in the saphenous system in my experience never causes pulmonary embolism except by extension into the deep femoral system. Therefore, this must be watched for carefully. I have seen two such patients die from fatal pulmonary embolism. One of them occurred after tying the saphenous vein following a warning benign embolism, when the femoral should have been ligated and sectioned. In the other, postmortem examination showed extension into the deep femoral system. If the phlebitis remains superficial, as it usually does, an ace bandage, rest off the feet but not bed rest, and sulfathiazole are the treatment of choice. If the phlebitis remains for a long time in one vein, one is justified in ligating this superficial vein well above the inflammatory process simply in order to isolate the lesion. Anticoagulant treatment may be used in especially stubborn cases as these cases may recur in migratory forms over months.

5. Thrombophlebitis in varicose veins rarely requires more than local heat, rest and compression bandages if not too painful. Pulmonary emboli do not occur from varicosities, and but rarely is there progression into the deep system.

6. Thrombophlebitis of the upper extremities is comparatively rare. I have seen only three cases. In one of these, multiple pulmonary emboli did occur. This case occurred in the days before heparin. The patient also had thrombophlebitis in the legs, and the source of the emboli may have been the leg or the pelvic veins. Some authorities declare this is a dangerous source of pulmonary embolism in the cardiac patient. However, I doubt if it is in younger people who have acquired the lesion from traumatic causes. The greatest danger is extension into the jugular vein or superior vena cava. Anticoagulant therapy and sulfathiazole are the treatment of choice. I see no reason why cervical sympathetic procaine block might not be used to reduce swelling. I do not believe that subclavian ligature is indicated except perhaps in the cardiac over fifty who has had a warning pulmonary embolism.

I have made no mention of leeches with which I have had no experience.

Conclusions

1. Deep phlebothrombosis of the femoral or calf venous plexi is a dangerous source of pulmonary embolism. If the patient is more than fifty, ligation and section of the femoral vein should be seriously considered. It cannot be emphasized too strongly in cases of this type that if there has already been a warning embolism, ligation and section of the femoral vein, or if need be, the external iliac vein, is indicated.

2. Phlebothrombosis in the pelvic veins is a dangerous source of pulmonary embolism. Prolongation of the clotting time by heparin or dicoumarin or both prevents propagation of a clot in the pulmonary artery should embolism occur.

3. In phlegmasia alba dolens, lumbar sympathetic procaine block is the treatment of choice. The earlier this procedure is performed the better, although the results obtained in chronic cases may be surprising. There is relatively little danger of pulmonary embolism in typical "milk-leg."

4. Thrombophlebitis migrans, thrombophlebitis of the upper extremities, and the thrombophlebitis of Buerger's disease rarely cause pulmonary embolism. However, propagation of the clot into the deep veins of the leg must be carefully watched for in phlebitis migrans. Isolation of an involved segment of vein by ligation may be necessary. Compression bandages, rest, and sulfathiazole are of value. Heparin or dicoumarin may be needed to stay progression of the clot in cases of thrombophlebitis in the upper extremities.

INTRACUTANEOUS INOCULATION OF POLIOMYELITIS VIRUS IN MONKEYS AND ITS DETECTION IN THEIR STOOLS *

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In order to learn if the virus of poliomyelitis can be detected in monkeys' stools after it has been inoculated intracutaneously the experiment presented in table 1 was performed. It may be described as follows:

On April 2, 1941, stools were collected from 10 monkeys representing four (or five) different species and one chimpanzee. The animals were then inoculated intracutaneously with the SK strain of virus (generation XIV) from monkey No. 17–66, a green African monkey. Injections were made in 10 piqures in the left flank with 2 c.c. of a 10 per cent suspension of glycerolated cord. The inoculated animals were placed in six separate cages according to species, and observed for the signs of experimental poliomyelitis. Daily rectal temperatures were recorded except for the chimpanzee which was exercised but not handled and which was kept in a separate building where there were no other infected animals. Thus the chances of unexpected contamination of stools were reduced with the chimpanzee. Stools were collected daily from each cage, refrigerated at 6° C. until a week's store was on hand, which was then pooled for storage according to species, and kept in an insulated box with dry ice. Green African monkeys [1] were used principally to test the stools for virus. For these tests 2 c.c. of 10 per cent stool suspensions were instilled intranasally on three successive days and at first 5 c.c. of etherized centrifuged suspension were also injected intraabdominally. With the first batch of seven stool tests there was an accidental loss of four green monkeys, and so in subsequent tests the intranasal inoculations alone were used as indicated in the legend of table 1. For controls a pool of all the preinoculation stools collected before the intracutaneous injections was tested in one monkey, and tests on preinoculation stools of three individual species (green and mona monkeys, and the chimpanzee) were also done. These controls appear in the first and second columns of table 1. In addition to tests with postinoculation stool suspensions, five tests of rectal swabbings (from monkeys 16–71, 18–13, 18–14, 17–98, and 17–99) by direct individual intranasal inoculations into three cynomolgus and in two green monkeys were made. These tests were negative and they appear in the column for the third week in table 1.

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† Deceased.

TABLE I

Intracutaneous Inoculation of Poliomyelitis Virus into Monkeys and Its Occasional Detection in Their Stools

Preinoculation Period Tests for Virus in Stools		Poliomyelitis Virus Inoculated Intracutaneously						Postinoculation Period Tests for Virus in Stools			
		Apr. 2, 2 c.c. 10% SK Strain			Experimental Poliomyelitis			Weeks After Inoculation			
General Pool	Individual Species	Species	Monkey No.	Cage	Paralysis	Remarks	Path. C.N.S.	1	2	2	4
		M. irus (Cynomolgus)	16–70	1	++	Died April 9	++	(−)*			
			16–71		−	Tuberculosis	−		−	−	
		M. mulatta	18–31	2	−	Tuberculosis	−	(−)	(−)		
			18–32		−	Tuberculosis	−				
(−)*		*M. irus* (*M. mordax*)	18–34	3	++	Dying, killed April 18	++	(−)	(−)		
			18–33		+		+				
	(−)	*C. mona mona*	18–13	4	+		§		(−)	−	
			18–14		+		+			−	
	(−)	*C. ethiops sabeus*	17–98	5	+		+	(+)*	(−)	−	
			17–99		+		0			−	
	−*	*Pan satyrus*	18–58	6		Agitation and tremor 2nd week	§	+*	+		−*

( ) Pool of stools of 2 or more monkeys.
§ Immune to reinoculation November 6, 1941.
0 Not examined.
* Intranasal and intra-abdominal inoculation.

The criteria for a positive stool test consisted in (*a*) the production of the usual signs of experimental poliomyelitis with flaccid paralysis of one or more extremities, and (*b*) the demonstration of classical histological lesions with vascular cuffing in upper and lower levels of the spinal cord. In the positive test with the first week's stools from the green monkeys, passage was also secured, and the virus used for this purpose was not infective for mice and guinea pigs on intracerebral inoculation.

The results shown in table 1 reveal that 14 of the postinoculation tests were negative and that three were positive. The virus was detected in the pooled stools of green monkeys 17–98 and 17–99, collected in the first postinoculation week and in the chimpanzee's stools collected in the first and second postinoculation weeks.

A comparison of intracutaneously induced poliomyelitis as given in the fourth column of table 1 records the fact that the most severe infections were among the cynomolgus and mordax monkeys. These two species appear much alike and they seem to fall under one designation (viz., *M. irus*) in Zuckerman and Fulton's manual,[2] and they have proved highly susceptible

in other experiments.[3, 4] Green monkeys 17–98 and 17–99 had typical mild paralytic poliomyelitis, and virus was found in their stools in the first week. The monas and one mordax had mild poliomyelitis and no virus was found in their stools. The mildest infection appeared in the chimpanzee, although her stool tests were positive twice. She had transitory agitation and tremor during the second week. She was able to walk normally and no paralysis could be made out on inspection, although at present she may have some atrophy of her hind legs. She has not been sacrificed. She was reinoculated seven months after her first inoculation and appeared immune, but the nature of this apparent immunity is not entirely clear. The test was as follows: she and a "normal" mate received the SK strain intracutaneously November 6, 1941 and developed no symptoms, although two normal cynomolgi and one normal mona contracted fatal poliomyelitis while the convalescent mona (18–13 of table 1) remained unaffected.

Returning to the experiment of April 2, the three tuberculous monkeys developed no signs of poliomyelitis, and we have noted before that tuberculous monkeys have been partially resistant to experimental poliomyelitis. It is therefore unfortunate for the sake of the comparative study that both the *M. mulatta* were tuberculous. Previously *M. mulatta* has proved less susceptible to cutaneous infection than the green monkey.[1]

Comment

When monkeys and chimpanzees have been fed poliomyelitis virus, it has been recovered from their stools or intestinal contents by Levaditi, Kling and Lépine [5]; Clark, Schindler and Roberts [6]; Clark, Roberts and Preston [7]; Flexner [8]; Howe and Bodian [9]; and Sabin and Ward.[10] After intracerebral inoculation, demonstration of the virus in stools of *M. mulatta* has failed according to Clark, Roberts and Preston [7]; and according to Howe and Bodian.[8] Virus was detected in upper intestinal contents of *M. mulatta* once, by Kramer, Hoskwith and Grossman,[11] but it is difficult to know whether this was after intranasal or intracerebral inoculation.

The present report is the first known to us of the detection of the virus in feces during the experimental disease apparently induced by intracutaneous inoculation. Possibly this indicates that the hands and thereby the mouths of the animals may have become contaminated. We do not hold this view, but even if it were true, the fact that virus may be applied to the skin and later detected in stools would still be important. However, it is unnecessary to postulate external contamination, because in another series of experiments (but not in this series) well marked lesions were found in the olfactory bulbs in one cynomolgus and one green monkey inoculated intracerebrally and intraabdominally but not intranasally with the SK strain. Moreover, Sabin and Ward [12] have detected the virus of poliomyelitis in the blood of cynomolgus monkeys paralyzed after oral infection with a strain

of recent human origin. Therefore, it appears that virus may spread in these species by paths as yet ill defined.

We believe that the positive results described in this report are dependent upon the particular strain of poliomyelitis virus used and the particular species of monkey tested. The results also suggest that the intracutaneous inoculation of virus may be a useful method for the comparative study of experimental poliomyelitis in different species.

Conclusion

1. Following the intracutaneous inoculation of the virus of poliomyelitis into monkeys it may be detected occasionally in their stools.

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THE ARMY'S NEW FRONTIERS IN TROPICAL MEDICINE *

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INTRODUCTION

THE United States Army is now engaged in an "all-out" war in the tropics. Since December 1941, American soldiers have been sent to new frontiers scattered throughout the tropical regions of the world. On these frontiers, they face powerful enemy forces and an alarming array of tropical diseases. Certain of these diseases are potentially so disabling that unless controlled they will interfere with military efficiency; in fact it is conceivable that they might play a significant rôle in determining the final outcome of the war. The protection of our troops against such diseases is, therefore, of vital importance, and the maintenance of an effective program for their control is a responsibility not only of the medical personnel of the armed forces but of the entire medical profession. With this common obligation in mind, it is proposed: (1) to define the term "tropical diseases"; (2) to indicate briefly the extent of the Army's past experience with such diseases; (3) to discuss the development of the present program for their control; (4) to estimate the effectiveness of this control program; and (5) to suggest certain ways in which it can be improved.

Definition of Tropical Diseases. According to Sawyer, "a tropical disease is any disease as it behaves in a tropical environment." His statement was modified as follows: "The natural tropical environment is not definable in terms of heat and humidity. It is really a thousand different and complex environments, occurring, to be sure, in the warmer parts of the earth, but compounded of special local conditions of climate, social make-up of the people, social and economic conditions, food materials and especially the arthropod vectors of disease and animal hosts."

This broad concept is excellent, but for our purposes it seems preferable to limit tropical diseases to the following categories: (1) diseases such as malaria, which may be endemic in either tropical or temperate climates, but are more prevalent in the tropics; (2) filth diseases such as the dysenteries and cholera, which are more common in tropical countries because of the poor sanitary, hygienic and climatic conditions which prevail in many such regions, but which may cause epidemics when introduced into temperate climates; (3) diseases which are normally limited to endemic centers in certain tropical regions, but may spread to and cause epidemics in temperate countries, as for

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example, yellow fever; and (4) diseases which originate in and are limited to tropical regions, as for example, African sleeping sickness.

The Army's Past Experience with Tropical Diseases. During the century and a half of our national existence, the Army has had a rich experience with tropical diseases both at home and abroad.

In the United States: In the Continental United States troops have always been exposed to such endemic diseases as the dysenteries, other enteric infections, and malaria. Before the present century, they were frequently attacked by epidemics of yellow fever, cholera, and other exotic diseases, introduced from abroad. Such infections have been most prevalent in the southern states, but at times they have occurred in the north. As is usual, they caused more damage during periods of war than in times of peace.

In Foreign Countries: Our soldiers have also been exposed to tropical diseases while on duty outside the United States. During the nineteenth century, such diseases were important causes of sickness and death among the American forces engaged in the Mexican and Spanish-American Wars. In the Mexican War, disease caused seven times as many deaths as did battle injuries. During General Scott's campaign in Mexico, the losses from disease alone exceeded 33 per cent of the effectual strength of his forces. The prevalent infections were dysentery, typhoid and malaria, but yellow fever and cholera were also present. During the war with Spain, we also lost seven men from disease to every one killed in battle. One-fifth of the troops developed typhoid fever, and this disease caused 80 per cent of the total deaths. Malaria produced a death rate of 2.7 per 1000 and after the capture of Santiago in 1898, it incapacitated half of our forces in Cuba. There were about 1500 cases of yellow fever with 200 deaths.

By the end of the nineteenth century a number of the causative agents of disease had been identified. Manson (1878) had discovered the mosquito transmission of filariasis; Theobald Smith and his associates (1892) had incriminated ticks as the vectors of Texas cattle fever; Bruce (1895) had identified the trypanosome of "nagana" in African horses and cattle; and Manson, Ross, Grassi and others had proved that human malaria is transmitted by Anopheline mosquitoes. However, the epidemiology of many infections was still unknown or imperfectly understood and military hygiene and sanitation were neither well-developed nor generally appreciated. This lack of basic medical knowledge was clearly reflected in the high infection and death rates.

During the 43 years which have elapsed since the Spanish-American War, great progress has been made in military tropical medicine. Immediately after the war, the United States acquired its first tropical possessions, and the Army established permanent garrisons in the Philippine Islands, Guam, Hawaii, Puerto Rico, and later in the Panama Canal Zone. Impressed with the health hazards to be encountered, George M. Sternberg, the Surgeon General, organized special boards of officers to study the diseases of certain of these newly acquired possessions.

The Board, formed by Walter Reed in Cuba, soon confirmed Carlos Findlay's experiments dealing with the mosquito transmission of yellow fever, thus indicating effective methods for the control of this disease. Richard P. Strong and the medical officers who succeeded him on the Board in the Philippines, including Craig, Vedder, Siler and others, made valuable contributions to our knowledge of cholera, the dysenteries, beriberi, plague, malaria, filariasis, dengue fever, and other diseases. Bailey K. Ashford in Puerto Rico showed that the local disease known as "Malignant Puerto Rican Anemia" was caused by massive hookworm infestation and started a control program which was a forerunner of the world-wide hookworm campaign conducted by the Rockefeller Foundation. Gorgas and his associates, armed with newly acquired knowledge about the mosquito vectors of yellow fever and malaria, were able to sanitate Havana and later the Canal Zone against these diseases; Russell at the Army Medical School produced an effective vaccine for typhoid fever; and Darnall developed a method for the chlorination of water supplies, which is now used in most of the large cities of the world.

These and other Army contributions and the innumerable researches carried on by other scientists all over the world afforded a valuable fund of basic information concerning the etiology, treatment and prevention of tropical diseases. With this information, it has been possible to develop methods for the protection of troops against infections both at home and abroad. Naturally these control methods were more effective under peace-time conditions in permanent garrisons than in the field during maneuvers or campaigns.

Since 1900 the Army has been increasingly successful in the control of all diseases including those of the tropics. During World War I, there was a temporary increase in the total disease rates due mainly to the influenza epidemic, but as our forces operated mainly in temperate regions, the only tropical disease of importance was malaria and this infection was well-controlled. However, as is shown in the following charts, there has been a spectacular decrease in the Army's peace-time admission and death rates for all diseases, and in 1939, these rates reached the lowest points ever experienced by the United States Army.

Development of the Present Program for the Control of Tropical Diseases. As the United States passed through the recent period of rapid mobilization into the present state of war, the Army acquired many new tropical frontiers. In 1940, when the Caribbean bases were obtained from Great Britain, our frontiers were extended to Bermuda, Jamaica, Antigua, St. Lucia, St. Kitts, Trinidad, and British Guiana. Since our declaration of war, they have been extended further by the transfer of military forces to other tropical countries in the Western Hemisphere and in Africa, Asia, Australia, the East Indies and elsewhere. Throughout this period the Medical Department has been actively engaged in the perfection of plans for performing all of its functions efficiently under such conditions as might

arise. Naturally, preventive medicine has had an important place in these plans. Arrangements have been made to strengthen all our existing health facilities by expansion, modification, or when indicated, by the adoption of

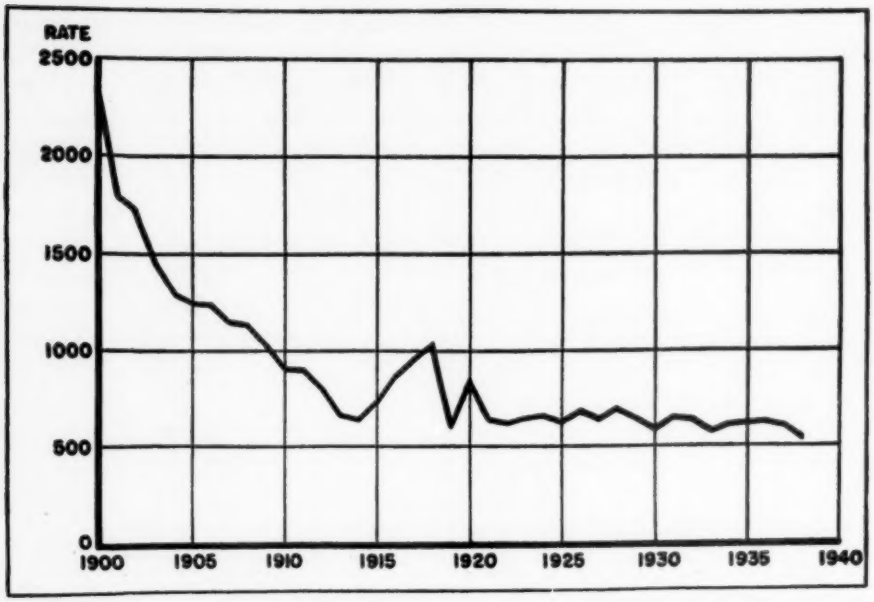

FIG. 1. Admissions, U. S. Army, 1900–1939. Admissions to sick report, officers and enlisted men, all causes excluding battle injuries, annual rates per 1,000 strength, since 1900.

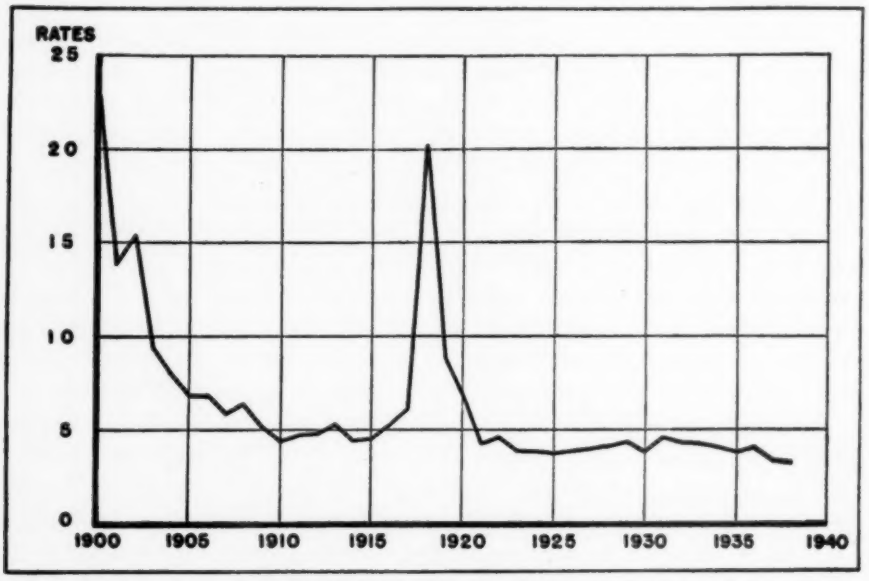

FIG. 2. Deaths, U. S. Army, 1900–1939. Deaths, all causes, excluding battle injuries, annual rates per 1,000 strength, since 1900.

new procedures. As our military interests spread to these new regions, greater special emphasis was placed on the control of tropical diseases.

Certain special features of the control program which has been adopted by the Surgeon General are indicated below:

(1) Since the early part of 1940, there has been developed in the surgeon General's Office, a special Preventive Medicine Service which now includes Divisions of Sanitation, Laboratories, Sanitary Engineering, Occupational Military Hygiene, Venereal Disease Control, Medical Intelligence, and Epidemiology. In the latter Division there is a subdivision devoted entirely to the control of malaria and other tropical diseases.

(2) The Division of Medical Intelligence was formed for the purpose of collecting and analyzing current information regarding medical and health conditions in foreign countries. Such information is obtained from every available source including the Pan-American Sanitary Bureau, the Rockefeller Foundation, other international and foreign health organizations and scientific publications. When possible, it has been supplemented by personal interviews with informed individuals and by the reports of sanitary investigations made by medical officers sent abroad for that purpose. The files of this Division now contain carefully prepared surveys on practically every country in the world. This information has been used by the Medical Department as a basis for specific sanitary precautions recommended for the protection of every military force which has left our shores. Such recommendations are naturally modified to meet the peculiar disease conditions of the regions to which troops are sent; for example, forces bound for certain parts of Africa would be warned against trypanosomiasis, whereas troops sent to Trinidad would require protection against the vampire bats of that region, of which about 4 per cent are vectors of rabies.

(3) A civilian advisory committee on tropical diseases was organized in May 1940, by the Division of Medical Sciences of the National Research Council. The members of the committee have rendered valuable advice on matters of policy and have assisted in the preparation of circular letters on tropical medicine for the guidance of medical officers throughout the service. They have also helped in planning our training program and in the initiation of various research projects dealing with tropical diseases.

(4) The Army's peace-time immunization program has been expanded to include vaccinations against certain diseases of the tropics. At present all military personnel receive the following prophylactic injections: (*a*) smallpox vaccine, (*b*) triple-typhoid vaccine, (*c*) tetanus toxoid, and (*d*) yellow fever vaccine. Personnel ordered to continents where they may encounter epidemic, or louse-borne typhus are given typhus vaccine; those going to regions in which cholera exists are given cholera vaccine; and in regions in which human epidemics of plague occur, plague vaccine will be used. Unfortunately, we do not know the degree of protection afforded by the typhus,

cholera and plague vaccines and, therefore, it is necessary to supplement the use of these agents by the strict enforcement of all other control measures.

(5) The expansion of the Army's laboratory services now includes special epidemiological and sanitary laboratory facilities in the tropics. An attempt has been made to staff these laboratories with individuals familiar with tropical problems, but unfortunately, such qualified personnel has not always been available.

(6) The health program has also been strengthened by the formation of the "Board for the Control of Influenza and other Epidemic Diseases in the Army." This Board is now composed of more than 100 civilian physicians. It is divided into nine Commissions, each dealing with a different problem. The Commission on Tropical Diseases is available at all times for the investigation of tropical infections.

(7) In 1940, a group of sanitary experts was organized to safeguard the health of civilians engaged in the construction of our Caribbean bases. A difficult medical problem was presented by the employment of the thousands of civilian workers required to build the air fields and other facilities needed to advance our frontiers over the Atlantic. The effectiveness of this program is shown by the fact that the construction has not been delayed by disease and there have been no epidemics among troops sent to these bases.

(8) A large number of research projects dealing with the prevention or treatment of important tropical infections have been initiated or sponsored by the Medical Department of the Army.

(9) An important part of the program has been the establishment of short "refresher" courses in tropical medicine at the Army Medical School and elsewhere.

An Estimate of the Effectiveness of the Present Control Program. When one considers the many regions to be occupied by American troops during this war, it seems probable that sooner or later our forces will be exposed to every known tropical disease. It would be foolhardy to attempt to predict the results of these exposures. However, one should be able to make a reasonable estimate of the situation from a brief review of the measures now available for the control of the more important diseases.

The *nutritional disorders,* particularly the vitamin deficiencies, including sprue, beriberi, pellagra, and night blindness, are prevalent in many tropical regions. Scurvy is less common but does occur. However, because of the extreme care exercised in providing a carefully balanced diet for American troops, nutritional diseases should not be a problem in our Army.

The *venereal diseases,* syphilis, gonorrhea, and granuloma venereum, are common in the tropics. The measures to be employed for their control abroad are the same as those used by the Army in the United States, namely, education, recreation, chemical and mechanical prophylaxis and treatment. In addition, special venereal disease control officers are now being assigned to Field Armies and Divisions, and prophylactic materials are furnished over-

seas forces. Human nature being what it is, we may expect an increase in the incidence of venereal disease among our troops wherever there is laxness in the administration of the control program.

The *food and water-borne diseases* occur in all parts of the world and, being diseases of filth, they are most prevalent in countries in which sanitary precautions are disregarded and soil and water pollution are common. Prior to the twentieth century these diseases constituted one of the most important causes of epidemics among military personnel, but thanks to the subsequent development of improved control measures they caused relatively little trouble during World War I. *Typhoid and the paratyphoid fevers* will be encountered everywhere, but all our troops are again protected by an effective triple-typhoid vaccine similar to the one used so successfully in the last war. The *dysenteries,* bacillary and amebic, are equally as widely distributed. Unfortunately, we have no specific measures for their control, but the methods of water purification as practiced in the field minimize the dangers of these diseases, and recent reports of the therapeutic usefulness of sulfonamides in bacillary dysentery are encouraging. It is hoped that more complete protection against bacillary dysentery can be afforded our troops as the result of investigations now in progress to develop an effective, non-toxic vaccine.

Cholera is now confined largely to its ancient endemic centers in Asia, where it continues to claim thousands of victims each year. However, on several occasions during the last century this dreaded disease spread over the world in great pandemic waves. These reached America and produced epidemics during the periods 1826 to 1837, 1853 to 1857, 1865 to 1868, and 1870 to 1873. As late as 1911, the disease reached the Port of New York, and during World War I it occurred in Russia, Austria, Hungary, Germany and Italy. Cholera is a real menace which cannot be disregarded. The Medical Department has provided a cholera vaccine which is being administered to all troops sent to areas in which the disease now exists. The degree of protection afforded by vaccination is not definitely known, and therefore the procedure must be supplemented by every available sanitary precaution.

Sanitation is paramount, and the Army has developed highly effective facilities for insuring safe water and food to the troops, even under field conditions. Therefore, these "filth" diseases should not occur in epidemic proportions among well-trained troops commanded by efficient officers, except under the most unusual circumstances.

The *insect-borne diseases* constitute a large group which includes some of the most dangerous infections to be encountered in the tropics. Potentially the most serious of these are plague, typhus, yellow fever and malaria.

Plague has ravaged mankind since antiquity. There were more than 100 epidemics or pandemics before the fifteenth century, and about 45 be-

tween the sixteenth and eighteenth centuries. During the Middle Ages, the "black death" killed one-fourth of the population of Europe, and 69,000 Londoners died of this disease in 1665. An epidemic began in Canton, China in 1895, and spread to Formosa, Japan, and India, where it continued until 1925, leaving twelve million dead in its wake. Between 1923 and 1924, 25,000 cases of plague were reported from epidemic areas throughout Africa, Greece, Asia, and several South American countries. The disease now smolders in great rodent reservoirs located in the western United States and elsewhere. From any of these places it may again attack man with epidemic fury. The measures adopted for the prevention of plague in the Army are based on the protection of troops against infected rodents and fleas, supplemented by the use of plague vaccine when required in regions in which the disease is epidemic in man. Information concerning the effectiveness of vaccination is inadequate, but intensive research on this subject is under way and it is hoped that agents of known prophylactic and therapeutic value will be developed.

Typhus fever is another ancient military scourge which has always been notorious for its production of destructive epidemics among troops. This highly fatal louse-borne disease occurs most commonly in temperate or cold climates but it also exists in the tropics. Moreover, it has been suggested that the milder, endemic or murine typhus of the warm climates might become epidemic by rapid passage through lice to man. This disease has been an important factor in almost every great war in Europe and recent reports indicate that it has again become active on many fronts.

The methods now available for the prevention of typhus are based on various sanitary and hygienic measures to prevent lousiness in troops, and the use of a typhus vaccine for forces going to certain regions in which the disease may be encountered in epidemic form.

Yellow fever also has an evil military record, especially in the Western Hemisphere, and prior to 1905 it frequently invaded the United States, producing highly fatal epidemics as far north as Philadelphia, New York and Boston. The disease is still endemic in vast jungle regions in tropical South America and Africa, and from these foci, the infection may at any time be carried by air or water to new areas where *Aedes aegypti* exist and produce epidemics in this country or elsewhere. Such outbreaks have occurred within recent years in Brazil and in the Anglo-Egyptian Sudan.

The Army's control program is based on (1) the enforcement of special precautions taken to prevent the introduction of the disease into our borders by military airplanes or otherwise, (2) the protection of troops against the bites of infected mosquitoes, and (3) the active immunization of all military personnel with yellow fever vaccine. This vaccine is prepared and supplied by the Rockefeller Foundation and the U. S. Public Health Service. Tests made subsequent to vaccination indicate that it produces a satisfactory immunity, and therefore it may be assumed that our troops will not suffer from yellow fever.

Malaria is the most widespread and the most dangerous disease to which our troops will be exposed. It is present throughout the tropics and subtropics of the entire world, and each year it causes more disability and deaths than any other infection. The Army has established an enviable record in its peace-time control of malaria among troops living in permanent stations even in our tropical possessions. During the recent mobilization, it has been possible to maintain this good record in the United States by the execution of an extensive mosquito control campaign, which in 1941 alone cost a million and a half dollars. We cannot hope for similar results among troops living in the field, even in this country, and must be prepared to meet the infinitely more dangerous problem of controlling malaria on our many new frontiers. Unfortunately we have no vaccine with which to immunize troops against malaria. Quinine or atabrin is provided for prophylactic use under certain conditions in the field. However, neither of these drugs is a real prophylactic, as they do not prevent infection but simply delay the appearance of clinical symptoms during their use. Therefore, the field control of malaria must be based primarily on the sanitary precautions required to protect men against infected mosquitoes. This is a difficult task but one which must be carried out thoroughly and unremittingly if the health of the command is to be maintained. One of the greatest medical contributions that could be made to this country at present is the discovery of a really effective agent for the prevention of malaria in the field.

Other insect-borne tropical diseases which may assume importance in various regions during this war include relapsing fever, filariasis, dengue and dengue-like fevers, Japanese river fever and other typhus-like diseases, Oroya fever, trypanosomiasis, leishmaniasis and other infections.

Theoretically, it should be possible to prevent all these insect-borne diseases by eliminating their vectors; but practically, this task is usually too enormous to be undertaken during the stress of war and under field conditions. Therefore, as only a few specific prophylactic agents are available, our chief reliance must be placed on the protection of individuals against insects.

Conclusion

From this general estimate of the situation, it is obvious that American troops will be exposed to an infinite variety of unusual and dangerous tropical infections during this war. It is also apparent that the degree of protection afforded our soldiers will depend on the ability of their medical officers to recognize the diseases clinically, treat them intelligently, and provide the sanitary and hygienic measures required for their control under trying field conditions. Such ability must be based on a sound fundamental knowledge of tropical medicine, including the epidemiology of tropical diseases. Since the beginning of the present emergency, the Surgeon General has been concerned with the fact that the majority of our new medical officers have not received adequate training in this subject prior to their en-

trance into the service. This lack of undergraduate training is being partially met by such emergency measures as the establishment of short, refresher courses in tropical medicine at the Army Medical School and in other Army establishments. But even this type of training is not available for all who require it, and the Army has neither the facilities nor the time to remedy so great an educational deficiency.

The solution to this problem is for the civilian medical schools to provide the required training for future medical officers. Short intensive courses in tropical medicine should be organized at once for the students of all medical classes which will graduate this summer and for the internes now in teaching hospitals. Action should also be taken to develop comprehensive courses in tropical medicine as a permanent part of the required undergraduate training in all of our medical schools.

Thus the medical educators of the United States have a unique opportunity to assist in the Army's program for the control of tropical diseases. If immediate steps are taken to provide satisfactory basic training in tropical medicine for all future medical graduates, this will not only raise the general level of medical education in this country, but will contribute materially to the safety of American troops on our new tropical frontiers.

A CONSIDERATION OF THE FACTOR OF CHANGE IN THE ANIMAL ORGANISM *

By Wm. deB. MacNider, F.A.C.P., *Chapel Hill, North Carolina*

Fixity of any order, even fixity of purpose, tends to bind and render inelastic the structure or the individual in which such a property develops. It is a quality which is inimicable to adaptation, and tissues or organisms without this quality of elasticity, of variability, have difficulty in meeting the exigencies of life which is made up of periods of adequate adaptation, never perfect, and periods of inadequate adaptation which may be of such a specialized nature as to produce the symptoms and later show the signs of disease.

Since 1907 the investigations in this laboratory have not been so much concerned with abnormal states as entities of disease as they have been interested in studying the changes associated with tissue degeneration and repair in a broad and, therefore, more helpful biological fashion. Certainly some of these changes may be looked upon as processes leading to adaptation, adaptation to advancing age and to maladjustments so marked that the departures from the normal have to be designated disease.

In thinking of the adjusted normal animal organism and the changes it can withstand one must conclude with a certain degree of assurance that the life span of such an individual was intended to be much longer than we now make it. I have said that "we now make it" for a purpose, for excluding physical accidents and accidents of an infectious order, the maintenance of life, its duration as well as its usefulness, are matters which we can in a large measure influence and in part determine. There are "factors of safety" within us with which we were endowed at birth that have been emphasized by Meltzer in his Harvey Society Lecture [1] for 1906. In this lecture Meltzer discusses our superabundance of tissues, far in excess of any normal demand, which through their cellular nature are endowed with the power either to increase in size upon demand or to increase numerically and further to impart to the individual great structural reserve power. This element of excess structure is furthermore shown in the dual character of certain organs and in the great power which organs, paired or unpaired, possess to take over function in the face of disease and carry on in an uninterrupted fashion the life of the individual as a whole. Such natural factors of safety have not been appreciated by us as reserves. Through excesses we have foolishly drawn upon them in their abundance for our normal way of life and depleted these factors of safety. Over-exercise, over-eating, over-worrying, more rarely over-drinking diminish these factors of endowed and natural safety, this abundant reserve tissue, and prepare us for

* Convocation Address, The American College of Physicians, St. Paul, Minnesota, April 22, 1942.

the advent of tissues so different from the reserve that we designate them pathological. However, even tissues of this order may safeguard us against ourselves by furnishing us an excess of tissue which, although altered, not only functions and in part adjusts us, but at the same time endows us with a factor of resistance against further injury. The human animal organism, even with the benefit of a physician as a biological guide, romps lavishly through these normal and abnormal tissue factors for safety. This is not the case with the lower animals. They run the race for food and for sport, experience the sensation of fatigue, and permit this sensation to exercise its function in a demand for rest. The factors of safety in our abundance of tissues are severely drawn upon in order to adjust and adapt us to an artificial and exorbitant type of life which we regard as normal. The most difficult life, the most unusual and pathological one, is a "normal" one.

In addition to the factors of safety found in the superabundance of our tissues as a whole and in specialized organ structure, the animal organism, by attempting to cope with adverse conditions, has acquired certain ways of life of a functional order, automatic, and in a sense reflex in nature, which afford further protection and persist in attempting to adjust us both within and without. Cannon [2] designates these forces "The Wisdom of the Body." This order of bodily, automatic thoughtfulness is not concerned with changes of a structural nature, but is concerned with maintaining the varied functions of the body in a balanced and in an effective state through an interrelationship of tissue activities. These functions have to be so related to one another within the living organism that a balanced and adapted existence can be maintained by the individual in that external environment in which he has to live. Many of these changes from within which lead to at least transitory periods of adaptation to external conditions in the course of life are effected through the intervention of that part of our nervous organization, the autonomic or vegetative nervous system, over which we fortunately have no control. The balance of electrolytes in the body fluids, the maintenance of a state of chemical neutrality during life, the fixity of a constant body temperature, the assurance of an adequate oxygen supply for tissue usage, all constitute adjustments resulting from change which favor a balanced existence. These and many other balanced functional states, favorable for life and capable of withstanding strain, are maintained in spite of our willfulness to the contrary. With the factors for safety of a structural order with which the animal organism is endowed, and over and above this the capacity of the body automatically to balance and adapt us to our environment, it would appear difficult for changes of such an order to take place as to injure us permanently by the development within us of gross chemical and structural alterations. Even in those states of tissue change which are designated disease there is evidence that we may become readjusted to them at certain modified levels of physiological effectiveness. There is an inherent urge on the part of cells, not for death, but for life. The changes of degeneration which many such units can withstand and their capacity for

recuperation and repair, if given an opportunity, constitute as a composite one of the major manifestations of life.

Some years ago, spurred on perhaps by the then actually non-existing state of prohibition, a period in which alcohol and aberrant alcohol beverages were consumed in large amounts, and at the insistence of certain life insurance companies, studies [3, 4] were undertaken in our laboratory to ascertain the effect of ethyl alcohol on the liver and to observe the changes during recuperation and repair if such developed in this tissue. Ethyl alcohol in 40 per cent strength was given once a day to dogs in a sufficient amount to induce a moderate degree of alcoholic intoxication. Such a procedure was continued for from six weeks to as many months. At periods during these intoxications tissue was obtained from the liver for histological study. Observation of the liver at such periods revealed large, pale organs from the abraded surface of which a blood-tinged serous fluid readily escaped. The microscopic studies of such tissues showed the presence of liver epithelial cells in an advanced state of edema, the fluid in such cells being held in lacuna-like spaces separated by strands of cell cytoplasm. Fatty changes in such cells existed but were not marked. The dominant cell change was of such a physicochemical order that the ability of the cell cytoplasm to bind water was greatly increased, the cytoplasm increased in volume, and thereby augmented the volume of the liver as a whole. From these observations it was difficult to believe that such an organ, by changes of cell recuperation or cell regeneration, could return to a normal organ structure, and yet the only factor necessary to lead to such a normal readjustment consisted in stopping the use of the chemical, in this instance alcohol, which had made the cellular structure of this organ undergo such a departure from its established normal. Here is an instance of a chemical substance modifying cell life in terms of its form in a very extensive and abnormal fashion, and yet this tissue is still able to return to a normal state of form and function. Such a recuperative change back to a normal type of cell is not associated with the development on the part of such cells of an acquired resistance to a subsequent injury by alcohol. The factor of safety which cells possess to repair themselves by processes of recuperation must be enormous and, furthermore, such changes must be constantly going on as tissues respond to injurious agents, recuperate and readjust themselves for normal function and thus for maintaining the life of the individual as a whole. Life necessitates cellular injury, and furthermore its successful continuance depends upon the ability of such injured units to recuperate rapidly by chemical change. This capacity for change is the main factor which determines longevity and which regulates tissue accidents that may express themselves in faulty organ adaptation. Chemical injury of a given order may be the stimulus for chemical action responsible for a continuation of cell life.

In addition to these experiments which have been presented, observations of a somewhat similar order have been made when the liver was injured by agents other than alcohol.[5, 6, 7] In these experiments the processes of repair

may be of such a nature that not only is a survival of liver tissue effected, but the liver tissue after repair may be shown to have acquired a fixed cell resistance associated with the changes in cell form that develop during the repair process. The change in cell form is not the essential element in this type of tissue resistance. The essential factor in it must be a modification of the chemical structure of the cell which is responsible for the permanent or transitory state of cell resistance.

Many years ago Whipple and Sperry [8] made the observation that if dogs were starved for 24 hours and then given chloroform by inhalation for one hour and a half, the livers of such animals invariably developed a severe injury in the form of a fairly complete necrosis of the central one-third to two-thirds of the liver lobules. Such a standardized reaction may be easily reproduced in experimental animals. There is another liver poison, uranium nitrate, which when given in an appropriate amount to animals of a susceptible age period [9, 10] induces a diffuse type of injury to the liver which involves all of the epithelial tissue of the liver lobules. Not infrequently this type of injury to the epithelial tissue of the liver as well as that of the kidney is both so severe and diffuse that the chemical and morphological changes of repair cannot be established. Such animals fail to survive. The order of change which uranium induces in the liver depends upon two factors, the age of the animal, and the dosage of this injurious agent. When these variables are properly adjusted either a slight or a severe structural injury may be established in the liver. Such injuries have certain quantitative functional expressions which are not very dependable, especially when they involve the use of some specific test for liver activity. The point of interest now under consideration, however, does not concern itself with quantitative functional expressions of injury. It does concern itself with what these slightly or severely injured cells do, what type of change they undergo during the process of repair. Responding to a slight or moderately severe injury, within eight days such epithelial cells effect a complete process of repair, either by recuperation or cell division with no change in the structure of such cells. The liver returns to its established normal structure. The rapidity with which constructive changes of repair can be effected in this organ is remarkable, and this in turn constitutes one of its factors for safety. If now such an animal be starved for 24 hours and be given chloroform for one hour and a half, this change or repair of the liver structure back to the normal is found not to have imparted any fixed epithelial cell resistance to the liver. These cells which had changed during the process of repair from degenerated types back to a normal order of cell are susceptible to the toxic action of chloroform and become injured, just as they would had the animal not been subjected to the epithelial injury by the use of uranium. If, however, the liver of an animal be more severely injured by uranium, and for this purpose older animals are selected, the outcome is different. In such animals the acute injury to the liver lobules is not only diffuse, but it is more severe than was the case with the former group of animals. In this latter group of animals which survive such a severe in-

toxication, the repair process is of a different type from that arising when a slight epithelial injury is induced. Such severely injured cells are incapable of establishing a state of repair through a process of recuperation without cell division. Furthermore, when changes within such cells have developed which permit and may also inaugurate cell division, the newly formed cells which result from such division are of an abnormal order. In place of being highly specialized in internal structure and polyhedral in form, they are a flattened type of cell and the cell substance frequently fails to show differentiation into cell entities. This changed tissue which results from repair, after an injury is atypical and abnormal in nature for this organ and resembles in some of its characteristics embryonic tissue. It has a functional value though less than that of normal hepatic tissue. It forms bile, stores glycogen, and removes from blood plasma certain dyes which may be used as an index of hepatic function. The observation of interest and significance in connection with this abnormal change in the liver resulting from a repair process is not the return of a satisfactory state of function, but the fact that such changed tissue has acquired a marked resistance to chemicals for which a normal type of cell in this location is highly susceptible. Such flattened, repair cells are resistant to chloroform, alcohol, carbon tetrachloride and uranium. Such an animal may now be starved, not for 24 hours, but for 48 hours, and given chloroform for two and one-half hours in place of one hour and a half without inducing injury or necrosis of the newly formed, functional, atypical cells of repair. A repair process, indicated grossly by a change in form which it is assumed has been associated with a change in the chemical nature of the cell, has led to the development of an acquired resistance to certain chemical agents which are invariably toxic for a normal order of liver cell. This same factor of change continues to operate in these cells which have acquired a transitory resistance. There appears to be a fixity of purpose in cells which manifests itself by a tendency of cell types to reëstablish their normal form. The abnormal type of resistant cell which has been described is not fixed nor static in its configuration. After some months it has a tendency to, or actually does, change back to a normal order of highly specialized hepatic epithelium. When such a change in chemical constitution has developed, these cells which have reverted back to the normal have lost their acquired resistance. This normal type of tissue is susceptible to the now injurious, degenerative effect of chloroform, uranium, carbon tetrachloride and alcohol.[11]

During the years over which these studies on form and changes in form have extended, a large number of senile animals have come under our observation. In a certain percentage of these animals, associated with the development of the senile state, there has occurred a change in the form of epithelial cell which is found in the liver. In such animals the specialized, polyhedral type of cell has been replaced by a flattened, atypical type, identical with that form of cell which may be induced to appear in the liver as a repair process when this organ has been sufficiently injured by some chemical agent. This naturally acquired shift in cell type associated with senility shows the

same order of resistance to chloroform, uranium, alcohol and carbon tetrachloride as is developed by severely injured cells during repair.

These changes in cell form as life adjusts and adapts itself to a variety of chemical experiences are impressive as they give to one a conception of the elasticity and adjustability of such changes ever tending to adapt an organ in which they occur and the organism, the individual as a whole, to life at some level of effectiveness. The observations lead one away from a concept of the fixity, the static nature and inelasticity of life processes, even when expressed as chemical equations within cells, as a form of life. It would appear that change is the essence of life and that an organ or organism, with the greater degree of adaptability to changed conditions is in turn the more likely to survive.

Finally and in summary, when we contemplate our varied factors for safety, for a continuation of life as an ever changing, shifting, yet balanced living entity, we may wonder at the brief duration of our life span. The duality of certain organs and the superabundance of reserve tissue in those not so paired, the ability of tissues automatically to throw into operation functional defense mechanisms, degenerative changes in tissues leading to processes of repair which afford tissue resistance, all tend to hold us not only in life, but in a balanced and, in some measure, an effective life.

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CASE REPORTS

PRIMARY TUMOR OF THE INFERIOR VENA CAVA AND HEART WITH HEMOPERICARDIUM AND ALTERNATION OF THE VENTRICULAR COMPLEXES IN THE ELECTROCARDIOGRAM *

By JOHN A. REISINGER, M.D., F.A.C.P., T. J. PEKIN, M.D., and BASIL BLUMENTHAL, M.D., *Washington, D. C.*

TUMORS of the heart, both primary and metastatic, are usually considered rare. Yater [1] summarized most of the literature up to 1931 and in the reports of authors quoted by him, the incidence of metastases to the heart varied from .02 per cent to 1.4 per cent of all autopsies and from 3.7 per cent to 7.5 per cent of all cases with malignancies. Scott and Garvin [2] noted series of cases published by Lymburner, by Pollia and Gogal and by Hellwig in which the incidence of tumors of the heart and pericardium varied from 0.2 per cent to 0.9 per cent of all autopsies and from 2.0 per cent to 6.0 per cent of all cases with disseminated neoplasms. In their own series of 11,100 autopsies, Scott and Garvin found 118 malignancies of the heart and pericardium among 1082 cases with malignant neoplasms elsewhere in the body or an incidence of 10.9 per cent. Our relatively small autopsy series composed of 355 cases examined in the last few years at this hospital included six cases with tumors of the heart and pericardium or a percentage of 1.7 per cent. This incidence is somewhat higher than in most of the larger series and is apparently not related to the number of lung tumors in the autopsied group (5.35 per cent) because in only one of these cases was cardiac metastasis noted.

Primary tumors of the heart, most of which are benign, are much less common than metastatic tumors. Hallack, Watson and Berman [3] have recently reported a primary tumor of the inferior vena cava and note that only four other such cases have appeared in the literature. In one of our cases, the lesion, which was unsuspected before death, proved to be a primary malignancy involving the inferior vena cava, right auricle, right ventricle, and the epicardial surfaces of the aorta and pulmonary artery.

A report of this case is presented both because of the rarity of the lesion and because of the unusual clinical manifestations associated with it.

CASE REPORT

C. N., a 45 year old colored barber, stated that he had been "fine" until his present illness and had never consulted a doctor although during the preceding year he had suffered from a number of vague complaints characterized by bloating, belching, palpitation and nervousness.

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About a week before coming to the hospital, the patient developed "cramps" in his legs after sitting on wet grass and shortly thereafter noticed that his legs were swollen. He became very dyspneic so that he could not climb a flight of stairs, and it seemed to him that his heart "dragged down" from the swelling. Oliguria was noted, although previously he had had nocturia two or three times nightly.

He continued to work as a barber until the night before admission when he suddenly felt faint and an hour later while at stool became completely unconscious. The attack was associated with profuse perspiration. After regaining consciousness, he went to bed and the following morning came into the hospital.

The patient was well nourished and well developed but appeared chronically ill. His breathing was rapid and shallow. The neck veins were distended to the angle of the jaw. The cardiac dullness was greatly widened both to the right and left; there was no visible pulsation of the heart. The heart sounds were barely audible and no murmurs could be distinguished. There was an arrhythmia of the heart, the character of which was not determined. Pulsations in the peripheral arteries were very small, and the blood pressure was 98 mm. Hg systolic and 78 mm. diastolic. No râles were heard on auscultation over the lung bases, although percussion suggested some pleural effusion bilaterally. The liver was palpated three fingers' breadth below the costal margin and there was ascites as manifested by shifting dullness. Edema of the lower extremities was marked.

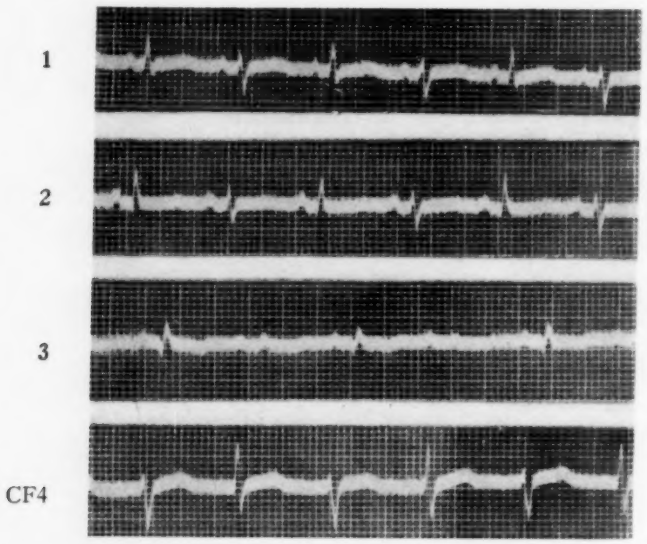

FIG. 1. Electrocardiogram taken day after admission to hospital showing alternation in QRS complexes of all leads.

An electrocardiogram (figure 1) taken the day after admission showed a sinus tachycardia with alternation in the direction of the QRS complexes in Leads I, II and IV F. In all leads the voltage was low, and in Lead III which was of particularly low voltage the QRS complexes alternated in amplitude rather than direction. There was nothing to indicate that the origin of the impulses varied in any of the complexes.

A roentgenogram of the chest taken on the same day with the patient erect and the tube at six feet showed a globular cardiac shadow greatly exceeding normal dimensions. There was a small amount of fluid in both costophrenic angles. The next day the patient was fluoroscoped in the upright position at which time very little

pulsation of the cardiac borders could be seen. The outline of the heart was traced in the standing and recumbent position without demonstrating any particular changes in the cardiac outline. A roentgenogram using a Bucky diaphragm (figure 2) was also taken in the recumbent position and, allowing for different tube distances, the shape of the heart shadow was essentially the same in the upright and recumbent positions.

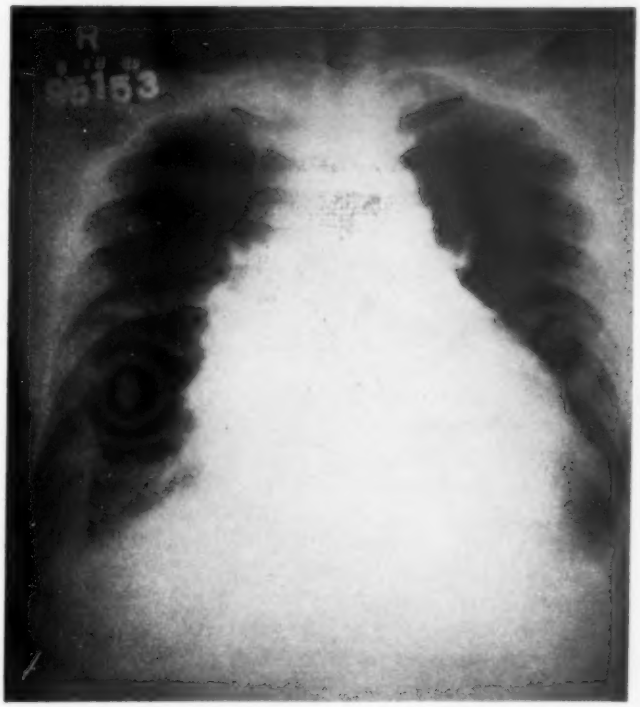

FIG. 2. Film taken using a Bucky diaphragm with the patient recumbent.

An electrocardiogram taken 10 days after the one described showed low voltage with slight alternation of the QRS complexes in Leads II and IV F. The alternation exhibited in this tracing was in amplitude, not direction of deflection.

The patient became progressively worse. His breathing was of the Cheyne-Stokes type. The edema, pleural effusion and ascites increased, and at times there were paroxysms of very rapid heart rate (187 per minute) interrupted by periods of slower rhythm (rate 120 per minute) when the electrocardiogram (figure 3a) showed a dominant sinus rhythm with frequent junctional premature contractions. An exploring electrode recording positivity in the electrocardiogram by an upward deflection was placed in the third interspace at the left sternal margin, and the tracing obtained (figure 3b) showed alternation of the QRS complexes. There was slight variation in the ventricular rhythm, and the P-waves preceding the deflections of higher amplitudes were either absent or deformed. This suggests that the impulses were arising from two foci in the supraventricular tissues at about the same rate, giving the appearance of alternation in this lead. During the paroxysms of more rapid rhythm, the electrocardiogram (figure 3c) taken with a chest lead as described above failed to show any P-waves, and alternation was not present. This was interpreted as a paroxysmal supraventricular tachycardia interrupted by periods of sinus rhythm with

junctional premature contractions. The alternation (figure 3b) when the rate was intermediate does not appear to be the same as that illustrated in figure 1.

The last electrocardiogram obtained from this patient did not show alternation in any form. The voltage was very low and QRS IV F was entirely minus except for a minute primary plus deflection (R).

The day after admission the patient's blood count showed 5,010,000 red cells, 5,300 white blood cells, and 15.5 gm. per cent hemoglobin. The non-protein nitrogen was 89 mg. per cent, and the blood Wassermann and Kahn reactions were normal.

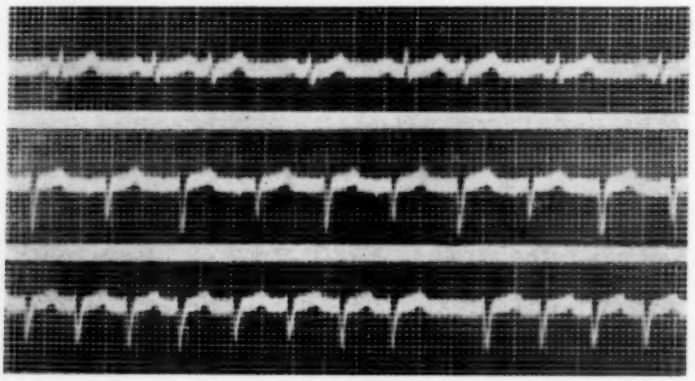

FIG. 3. Electrocardiogram taken during successive phases of tachycardia. a. Lead I. b. Chest lead with chest electrode placed in third interspace at left sternal border and indifferent electrode on left leg connected so that positivity beneath the chest electrode causes an upward deflection in the electrocardiogram. c. Same as b. during paroxysm of tachycardia.

It was agreed that the patient had a pericardial effusion with cardiac tamponade without any of the usual causes to explain it. A paracentesis of the pericardial sac was attempted about 10 days after admission to the hospital. The needle was inserted posteriorly beneath the angle of the left scapula in the ninth intercostal space. Clear straw-colored fluid was obtained from the pleural cavity and upon inserting the needle slightly deeper, blood was obtained. About 20 c.c. were withdrawn and although there was no definite bumping of the needle, the operator was not sure that he had not entered a cardiac chamber so the procedure was discontinued. The patient made no complaints and exhibited no untoward signs during or immediately following the paracentesis. It was noticed that the blood which had been withdrawn did not evidence any tendency to clot in the 30 minutes or more before it was sent to the laboratory for guinea pig inoculation. Neither the blood nor the pleural fluid produced a tuberculous reaction in guinea pigs.

The patient's condition became progressively worse and he died on July 20, 1939, 25 days after his sudden collapse and about five weeks after the first symptoms of congestive failure.

Autopsy: Both pleural spaces contained approximately 1500 c.c. of clear, amber-colored fluid; the lungs were partially collapsed. No evidence of pulmonary tuberculosis was noted. There was a moderate amount of fluid in the peritoneal cavity, and the liver was not particularly enlarged. It was generally pallid, although thick blood exuded from the cut surface.

The pericardial sac occupied a large part of the thorax. It was tense, bluish black, and contained over 2000 c.c. of blood. This was not clotted but the red cells had largely settled into the dependent portion of the sac, leaving a syrupy, bile-colored plasma on the surface. The heart was not enlarged; in fact, the muscle substance seemed decreased and the chambers contained no clot. On the anterolateral aspect of

the inferior vena cava, just before opening into the right auricle and within the pericardial sac, there was a bulging mass about 2 by 3 cm. in dimension which appeared to be an organized clot. There was a rupture in the wall of the vessel 1.5 cm. long which the mass largely occluded. On opening the vena cava this friable, thrombus-like substance extended through the wall of the vessel and involved a somewhat larger area on the inner surface. There was a definite thickening of the caval wall which extended into the auricular wall, forming a crescentic raised ecchymotic area on the endocardial surface. There were other smaller, discrete nodules projecting slightly on the endocardial surface of the auricle and one in the right ventricle beneath the tricuspid valve. Over the pericardial surface of the aorta and pulmonary artery, and particularly in the epicardium between these two structures, there were bleb-like elevations about 1 cm. in length which contained soft, bloody material.

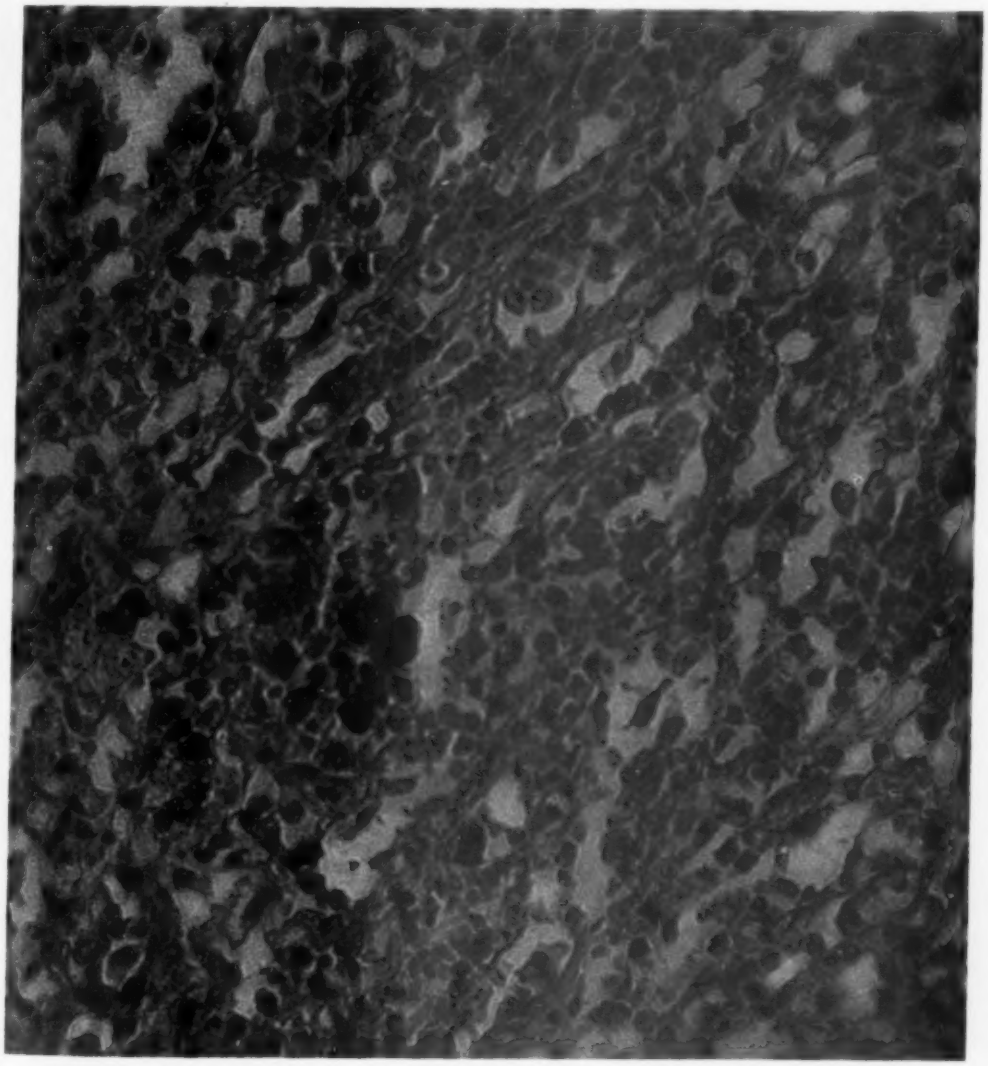

FIG. 4. Section through the wall of the inferior vena cava showing structure of the tumor and types of cells present.

The other gross findings in the autopsy were not particularly significant. No tumor was found in any other portion of the body.

Histology. A section through the rent in the inferior vena cava (figure 4), including the mass and the adjoining "normal" portion of the inferior vena cava, revealed marked disorganization of the wall due to widespread hemorrhages of different sizes and ages and infiltration by cells of many types.

The background for the infiltrating cells was, for the most part, the spread fibers of the vessel wall and in some places a newly formed, loosely packed connective tissue stroma. Diffusely spread through its meshes were many freshly extravasated red blood cells. Many of the erythrocytes were fused in the process of destruction and an abundance of hemosiderin was seen in phagocytes.

The infiltrating cells were widespread, numerous, rather loosely packed and showed variation in size, shape and staining qualities, but fell into three main groups:

Group 1. One very common cell was rather irregularly elongated, measuring about 12 μ by 5 μ, with a large, round or oval nucleus containing a pale nuclear sap. One nucleolus and several strands of chromatin were seen regularly. The cytoplasm, seen with difficulty, was rather scanty, stained faintly eosinophilic and contained no granules.

Group 2. Almost as common was a cell roughly polygonal or circular in shape about 12 μ in diameter with an eccentrically placed bean-shaped nucleus which was homogeneous and slightly pink staining. The nucleus filled more than half the cell, and its concavity was directed toward the larger cytoplasmic mass which stained lightly neutral and contained no granules.

Group 3. There was a scattering of lymphocytes, polymorphonuclear leukocytes (mature fibroblasts), and an occasional eosinophilic leukocyte.

None of the cells was arranged like a glandular structure or in any other regular manner. Many of the large cells (group 2) had two or three nuclei, but active mitosis was not recognized. There was no fibrosis.

The wall of the right auricle (figure 5) showed the same extensive hemorrhage and invasion by exactly the same sort of cells and in about the same proportion as described for the inferior vena cava. There were several differences, however, apparently due to the dissimilarity in structure of the vena cava and auricle:

(1) No subserous fat was seen, but the epicardial fibrous layer was distinct. The "tumor" extended to this structure but did not penetrate it. One limited area showed raising of the mesothelium by an accumulation of erythrocytes and lymphocytes. No fibrin overlaid the epicardium.

(2) In the myocardium, dying muscle fibers were easily recognized. Some were slightly enlarged, but for the most part they were atrophic and seemed to be dissolving. In areas away from the most active part of the "tumor" the myocardium showed degeneration and atrophy (pressure?) but there was a distinct fibroblastic response here and some fibrosis. In the most active part of the lesion muscle fibers could not be recognized.

(3) The "tumor" invaded the subendocardium, and in localized regions growth was uneven, the endothelium being thrown up into large finger-like projections covering a central core of new growth. In such "villi" lymphocytes were common, but cells of groups 1 and 2 were also seen spread through a loose stroma. Hemorrhage was slight and not very recent. No thrombus was attached to the endocardium.

A section taken through one of the isolated blebs in the adventitia of the pulmonary artery showed an extremely hemorrhagic, circumscribed lesion made up of the same types of cells noted in the caval and right auricular tumors. The lesion was limited to the adventitia, the media being normal except for one area in which a small,

homogeneous, hyaline, acellular zone of necrosis was seen. In the adventitia, however, the tumor had led to the destruction of the periarterial nerves and obliteration of many of the vasa vasorum (which may explain the zone of medial necrosis). The intima showed no abnormalities and the endothelium was intact.

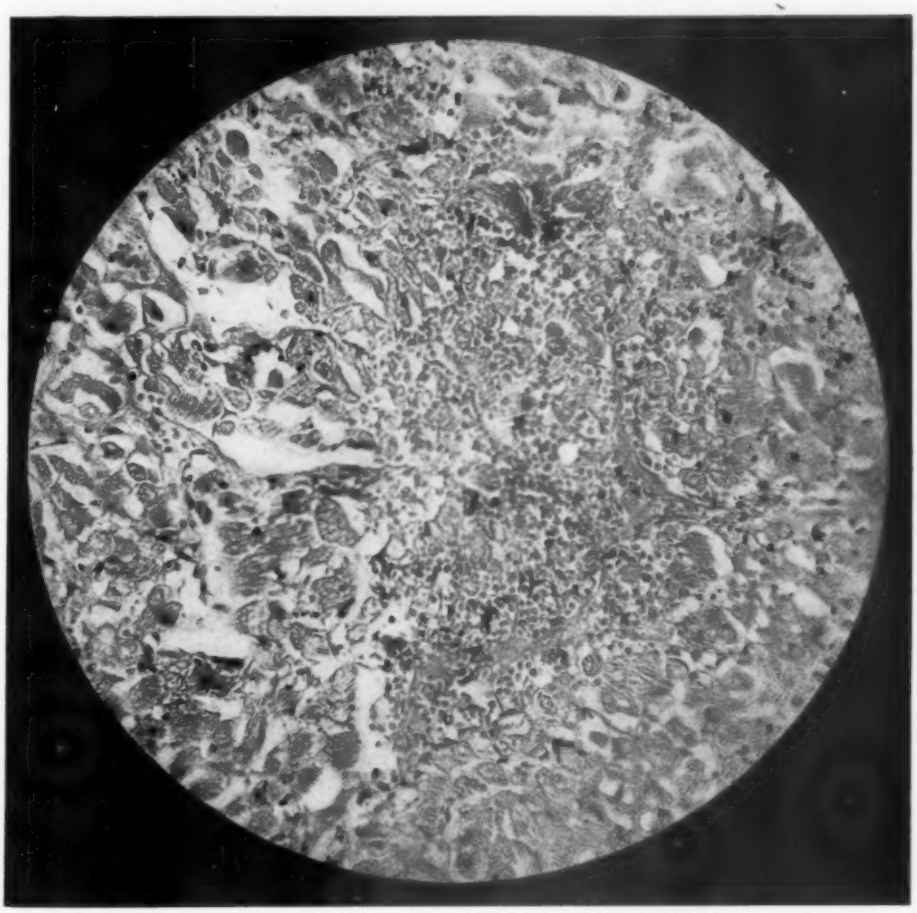

FIG. 5. Section through wall of right auricle showing invasion of the myocardium by the tumor.

A section through an apparently normal portion of the left ventricular wall at the base of the heart showed a considerable submesothelial infiltration of the subserous fat by hemosiderin laden phagocytes and many small lymphocytes. No tumor cells were seen. Except for early changes of sarcolytic degeneration and some infiltration of the interstitial spaces of the myocardium by mononuclear eosinophiles and fibroblasts, the heart muscle was normal. The endocardium was intact throughout.

The nature of this lesion of the inferior vena cava and right auricle is uncertain. It has been suggested by those who have examined the sections that the lesion might represent chronic inflammatory reaction, sarcoma or endothelioma. The difficulty in distinguishing among these three is recognized by Ewing[4] who,

in his discussion of endothelioma, states that "Vascular endothelium also proliferates readily in inflammation and forms collections of cells which may resemble the groups of endothelioma or carcinoma," and again, "The studies of recent years have served chiefly to emphasize the difficulty of separating true endothelioma from many typical sarcomas, lymphosarcomas, carcinomas and certain embryonal tumors."

We are inclined to believe that the lesion in our case is an endothelioma because of: (1) the origin of the tumor in the wall of a blood vessel; (2) the rather primitive, mesenchymal appearance of the cells; (3) the multiplicity of the lesions—discrete nodules were found in the inferior vena cava, right auricle, right ventricle and adventitia of the aorta and pulmonary artery; (4) the low grade invasiveness of the tumor.

Comment

Tumors of the heart, even when of great size, often produce no functional disorders, a fact which precludes an estimate as to how long the neoplasm had been developing in our patient. It is quite probable that the onset of symptoms corresponded with the rupture of the vena cava resulting in cardiac tamponade from the hemopericardium. Hemorrhage into the pericardium occurs occasionally in dissecting aneurysm and myocardial infarction as a terminal event, but survival for any prolonged period of time is unusual. Our patient lived about five weeks after the onset of symptoms and during part of this time he was ambulatory. Rixford [5] described a case in which the patient lived about nine weeks following trauma that caused rupture of the right auricle with hemopericardium. McNamara [6] reported a case with metastatic carcinoma of the auricle which ruptured. This patient had an accentuation of his cardiac symptoms 17 days before death, presumably at the time of rupture. The duration of survival must depend largely upon the underlying pathology in the heart and the rapidity with which blood is lost from the circulation, which also governs the degree of tamponade. In most instances, except when the hemopericardium is due to trauma, the duration of survival may be largely of academic interest, but the possibility that intrapericardial rupture may not be immediately fatal must be considered in diagnosis. The relatively low pressure in the vena cava and the partial obstruction of the rupture by thrombus formation probably accounts for the prolonged course in our case.

Another unusual feature was the alternation of the QRS complexes in the electrocardiogram during a part of this patient's illness. It has already been noted that there was at different times an alternation both in the direction and shape of the QRS complexes and also in their amplitude. The alternation in amplitude illustrated in figure 3b is probably due to regularly recurring impulses arising in the junctional tissues alternating with impulses from the sino-auricular node. Although the QRS complexes with the highest amplitude were not regularly preceded by distinguishable P-waves, these complexes did not always occur prematurely and were not always followed by longer R-R intervals as might be expected with premature contractions.

As contrasted with this alternans the type exhibited in figure 1 occurs in a regular sinus rhythm, the direction of the principal deflections in alternating complexes being exactly opposite except in Lead III where the amplitude is low.

Brody and Rossman [7] state that differentiation should be made between electrical alternans and bidirectional complexes which our case seems to show. It differs from the case presented by Smith [8] to which they refer, however, in that the rhythm is of sinus origin rather than an ectopic ventricular rhythm and the R-R intervals are constant. Hamburger, Katz and Saphir [9] quote Kisch [10] to the effect that electrical alternans may consist of variations in either the amplitude, contour, duration or direction of the involved complexes. In this sense the electrocardiogram reproduced in figure 1 can be considered an example of electrical alternans.

Electrical alternation is generally considered an expression of the mechanical behavior of the ventricles and may, therefore, be associated with a pulsus alternans. We did not observe this phenomenon in our patient but cannot be sure it was not present. The usual view concerning mechanical alternation is that the weak beat is weak because fewer muscle fibers contract. Lewis [11] suggests that in alternation all regions of the muscle contain defective fibers, the concentration of which is greater in some regions than another; thus, under certain circumstances the defective fibers might participate in the contraction of the ventricle only on alternate beats. He thinks that "The order in which muscle elements are activated would not be disturbed in these circumstances," and in his experience "The change and variations in the electrocardiographic curves of axial leads are too small to be compatible with the failure of relatively large and solid masses of ventricular substance." The shape of the complexes in our case, however, suggests an alternating pathway for the ventricular wave of excitation or an alternating relationship of the heart in space to good conductors. Brody and Rossman [7] also suggest that "alternation may be due either to two alternating foci of impulse formation or to two alternating paths of conduction from one focus." A more gradual phasic variation of the electrocardiogram may occur normally with respiration, and Hamburger et al.[9] noted slightly alternation for one to three cycles related to inspiration in one of their cases. To produce the regular alternation at the rapid heart rate noted in our case would presumably have required a very rapid respiratory rate which the patient did not exhibit, although graphic records of respiration were not obtained.

All authors agree that alternation is observed only when "The muscle is laboring and in difficulty" and that it indicates a very unfavorable prognosis. Experimentally [11] it has been produced by increasing the cardiac rate, by administering various poisons such as digitalis, antiarin, aconite, glyoxylic acid and hemolytic serum, and also by occluding a coronary artery. Clinically, coronary arteriosclerotic heart disease is most often the underlying disease when alternans is noted. Our patient presented no unusual damage of the coronary arteries or the ventricular myocardium. The large hemopericardium with tamponade undoubtedly did interfere with myocardial nutrition and may have been responsible for the transient alternans noted in the electrocardiogram. Feldman [12] reported a case with serosanguinous pericardial effusion from carcinomatous metastasis in which alternans was observed in an electrocardiogram obtained shortly before death. He assumed that the electrocardiographic abnormalities were due to myocardial changes resulting from interference with the coronary circulation by the tamponade. Harvey and Whitehill [13] also noted "alteration in amplitude was occasionally observed as was change in the form of each second or third complex" in tuberculous pericarditis with effusion.

It is to be noted that alternation was only a transient phenomenon in our case, a characteristic usually noted by others. This was true in spite of the persistence of the tamponade and, therefore, the disappearance of the electrical alternans did not indicate an improvement in the heart muscle but perhaps a more generalized depression of all the muscle fibers so that their function was equally poor. Although the location of the lesions in the right auricle suggests the possibility of aberrant excitation waves and the unclotted blood in the pericardium might have alternately affected conduction from the heart, the best explanation for the electrical alternation probably is that it depends upon functional myocardial changes resulting from coronary insufficiency.

Summary

A case is presented in which rupture of the inferior vena cava with hemopericardium occurred. This rupture traversed a lesion in the wall of the vena cava which in our opinion was an endothelioma. Similar growths were found in the wall of the right auricle, right ventricle and the epicardial surfaces of the aorta and pulmonary artery. The patient survived the rupture of the inferior vena cava for at least 25 days, and during the course of his illness the electrocardiogram exhibited electrical alternans on several occasions.

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HYPERPARATHYROIDISM WITH CALCINOSIS AND SECONDARY TO RENAL DISEASE; REPORT OF A PROBABLE CASE *

By L. E. CURTIS, M.D., *San Francisco, California,* and A. E. FELLER, M.D., *Iowa City, Iowa*

HYPERPARATHYROIDISM [1, 2, 3] is usually due to an adenoma of one or more of the parathyroid glands, but occasionally it may be due to diffuse hypertrophy (hyperplasia?) † of all parathyroid tissue.[4, 5] The adenomata [6] may be composed of one dominant cell type or of a mixture of cell types, but the hypertrophic glands are uniformly composed of large cells with clear cytoplasm, the so-called large ‡ "wasserhelle" cells. The distinction, however, is purely on the basis of the anatomical alterations in the parathyroid glands since the resultant disease is similar. Renal complications are common.[7] For example, in a survey of 83 patients with hyperparathyroidism, Albright, Baird, Cope and Bloomberg [8] found 23 with renal lithiasis, one with acute renal insufficiency, and 19 with calcium precipitation in renal tubules with resulting renal sclerosis, contraction and insufficiency.

The above relationship, primary parathyroid disease followed by renal alterations, is well known. The reverse of the sequence of events, primary renal disease followed by secondary (compensatory?) hyperplasia of all parathyroid tissue is also well recognized.[7] Although the exact mechanism is not known, there is experimental evidence to show that the parathyroid hyperplasia is secondary to the renal disease.[9] It is probable that the degree of parathyroid hyperplasia is roughly proportional to the length of time renal insufficiency has been present [9, 10, 11] and that excessive enlargement, often accompanied by alterations in the bones, is most probably the result of severe renal insufficiency of long duration.[11] As Albright, Drake and Sulkowitch suggest,[11] the fact that renal insufficiency does not usually last for a long time probably explains why marked secondary parathyroid enlargement is not common.

The anatomical alterations of the parathyroid glands in secondary hyperplasia are reviewed by Castleman and Mallory [10] who suggest exact criteria for the diagnosis of the condition. They find that all of the glands show varying degrees of gross enlargement, that they are composed principally of normal sized chief cells, that the oxyphil cells are always greatly increased in number, and that a few small water-clear (wasserhelle) cells are occasionally present. It should be added, however, that the parathyroid hyperplasia secondary to renal disease does not seem to differ qualitatively from that present in a variety of other conditions.[10] Furthermore, Castleman and Mallory [10] state: "It is remotely possible that localized, adenoma-like hyperplasia is occasionally the response of the parathyroid glands in secondary hyperplasia."

From available data, as Albright, Drake and Sulkowitch [11] suggest, it appears that the following three conditions occur: (1) primary hyperparathy-

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From the Department of Internal Medicine, State University of Iowa, Iowa City, Iowa.
† For a discussion of hypertrophy vs. hyperplasia see reference 5.
‡ In contradistinction to small "wasserhelle" cells seen in secondary hyperplasia, as will be noted later.

roidism due to adenoma and predisposing the patient to renal disease; (2) primary hyperparathyroidism due to idiopathic parathyroid hypertrophy (hyperplasia?) and, likewise, predisposing the patient to renal disease; and (3), primary renal disease which, if it is severe and of long duration, may lead to parathyroid hyperplasia and, occasionally, to osteitis fibrosa generalisata.

Recently Albright, Drake and Sulkowitch [11] described an apparently rare syndrome which they named renal osteitis fibrosa cystica. The outstanding features of the syndrome are marked renal insufficiency that has lasted for a long time, phosphate retention in the blood with a high blood serum inorganic phosphorus level, slight reduction of the blood serum calcium level, marked acidosis,

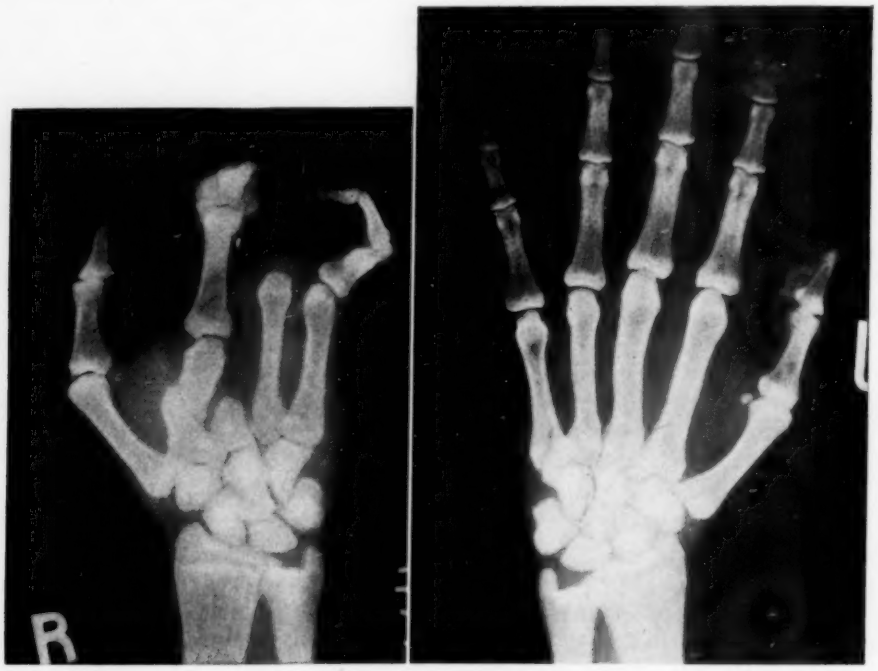

FIG. 1. Roentgenograms of the hands.

calcium deposits in the neighborhood of joints, extreme calcification of the media of arteries (Mönckeberg type), osteitis fibrosa generalisata of all bones, and enormous enlargement of all parathyroid tissue. Their patient had renal disease for 23 years; there was severe renal insufficiency; the serum calcium was 8.2 mg. per cent and the serum inorganic phosphorus 9.8 mg. per cent; and roentgenograms revealed definite osteitis fibrosa generalisata and many areas of calcium deposition about joints. At necropsy all four parathyroid glands were tremendously enlarged and consisted essentially of chief cells. The authors believe that the condition is the adult counterpart of renal rickets in children, that the renal insufficiency is primary, and that the other features are secondary, the prime requisite being that the renal insufficiency be present for a long time. The parathyroid hyperplasia is believed to be secondary to the phosphate retention occasioned by the renal insufficiency. The osteitis fibrosa may be a

result of the excess of parathyroid hormone but, in the opinion of these authors, a more likely explanation for the pathogenesis of the bone changes is a lack or decrease of calcium absorption from the intestinal tract with a slightly increased resorption of bone due to the acidosis. Calcium balance determinations performed upon their patient are cited to support this latter contention. The explanation for the deposition of calcium around the joints, the feature of the disease which makes it unique, is not clear, but it is suggested that it might be due to the presence of an excess of colloidal calcium phosphate which is quickly removed from the blood. Briefly stated, renal osteitis fibrosa cystica appears to be an extreme and unusual example of parathyroid disease occurring secondary to renal disease (group 3 as discussed above), the outstanding feature being the curious deposition of calcium about the joints.

We wish to report a patient who presented the necessary clinical criteria for a diagnosis of renal osteitis fibrosa cystica, or secondary hyperparathyroidism, but who, in the final analysis, could have had quite the opposite condition, namely, primary parathyroid disease. A difficult and practical problem in differential diagnosis is the result.

Case Report

W. O., a white male, aged 40, entered the University Hospital on July 14, 1938. He complained of distress in the region of the joints, abdominal discomfort, headaches, "abscesses" of the finger tips, a mass on the right side of the face, generalized pruritus, and nocturnal diuresis. His history revealed that he had suffered from

Chart I

Blood Chemical Data

Date	Urea N mg. %	Creatinine mg. %
7/14/38	95.2	6.6
7/17/38	91.0	7.4
7/24/38	96.6	8.6
8/1/38	96.6	10.9
8/8/38	92.4	8.4
8/16/38	84.0	6.7
8/23/38	86.1	6.7
8/30/38	88.2	7.5
9/13/38	88.9	7.1
10/3/38	130.2	10.5
10/5/38	145.6	8.4
10/7/38	130.9	7.8
10/11/38	139.3	8.5
10/14/38	105.0	8.3

Plasma Proteins (gm./100 c.c.)					Plasma Chlorides mg./100 c.c.
Date	Fib.	Alb.	Glob.	Total	
7/14/38	—	3.08	3.17	—	638
7/17/38	.51	3.17	2.57	6.25	575
10/11/38	.81	2.72	2.82	6.35	

Date	Serum Calcium mg. %	Serum Phosphorus mg. %	Phosphatase (Bodansky units)	Alk. Res.
8/30/38	11.1	7.7		
9/13/38				45 c.c.
9/15/38	10.9	10.2	14.4	
10/3/38				43 c.c.
10/5/38				49 c.c.
10/7/38				58 c.c.
10/11/38	12.2	10.0	10.8	
10/14/38				33 c.c.

vague abdominal distress and flatulence for 16 years. In 1926 the right knee became enlarged, hot, tender and very painful for four days, but he was able to resume work in 10 days. During the six year period prior to the time he came to the hospital he noted, intermittently, sharp, shooting pain over the kidney regions when stooping. Blurring of vision had been present for three years. Soon thereafter his physician found pus and albumin in the urine. The albuminuria persisted. In the fall of 1937

he became very weak. In May 1938, following exposure in the rain, he developed an acute delirium and thereafter his finger tips became enlarged and tender, a mass appeared just anterior to the right ear, and generalized pruritus began. In June, 1938, headaches appeared, the knee joints became painful, and there was a marked increase in weakness and fatigability. About one week before he came to the hospital the shoulder joints became painful and nocturnal diuresis, which had averaged four or five times for several months, increased to eight or nine times.

He appeared chronically ill and pale. Scattered over the entire body, but most pronounced on the exposed surfaces were many brownish-black pigmented areas

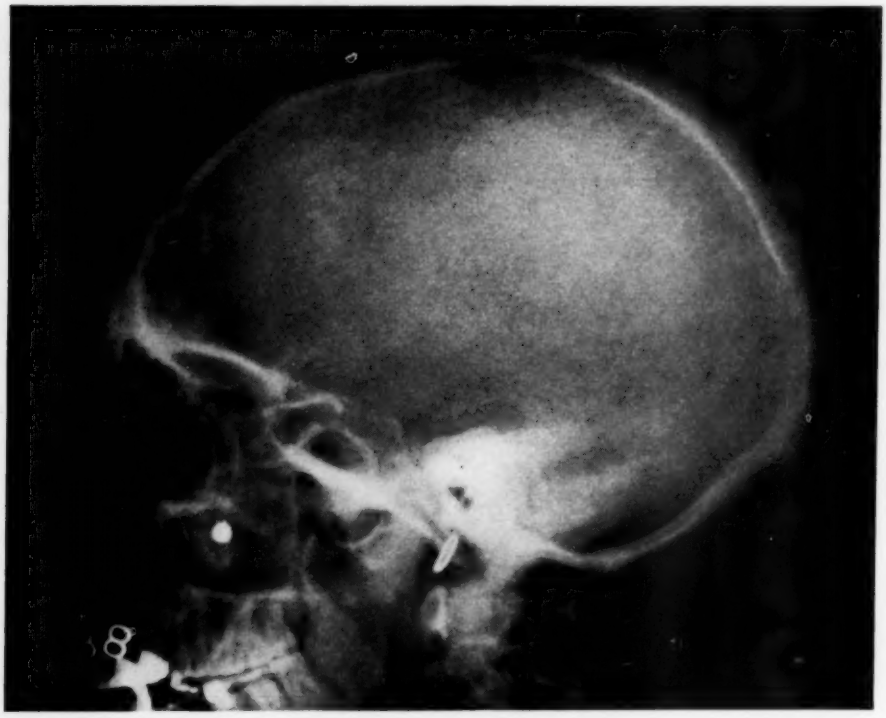

FIG. 2. Roentgenogram of the skull.

which were, on the average, 1½ mm. in diameter. Examination of the ocular fundi revealed slight, generalized diminution in the caliber of the arteries and the absence of hemorrhages or exudates. A firm, rounded, smooth mass, measuring 3 by 3 by 1 cm., was present just anterior to the right ear. It was only slightly tender, it was not fixed to the skin, and it was not adherent to the underlying bone. There was no lymphadenopathy. The thyroid gland was not palpable and no masses could be palpated in that region. The extensibility, volume, and density of the lungs were normal. The left ventricle of the heart was moderately enlarged and the arterial blood pressure was 145 mm. Hg systolic and 95 mm. diastolic. The peripheral arteries were not tortuous but their walls were definitely thickened. No masses or solid organs were palpable in the abdomen. The prostate gland was moderately enlarged. The second and third fingers of the right hand were absent, the result of an accident early in life. There was a bulbous, firm but fluctuant swelling of the second joint of the right index finger. A similar mass was present over the dorsum of the right hand. The right

little finger, the left thumb, and the left index, middle, and little fingers presented bulbous, firm, and slightly tender swellings of the terminal phalanges. The toes were normal. The neurological examination revealed no abnormalities.

The urine consistently had a low specific gravity which varied between 1.001 and 1.013, was alkaline to the litmus paper test, and contained 5 to 6 grams of protein

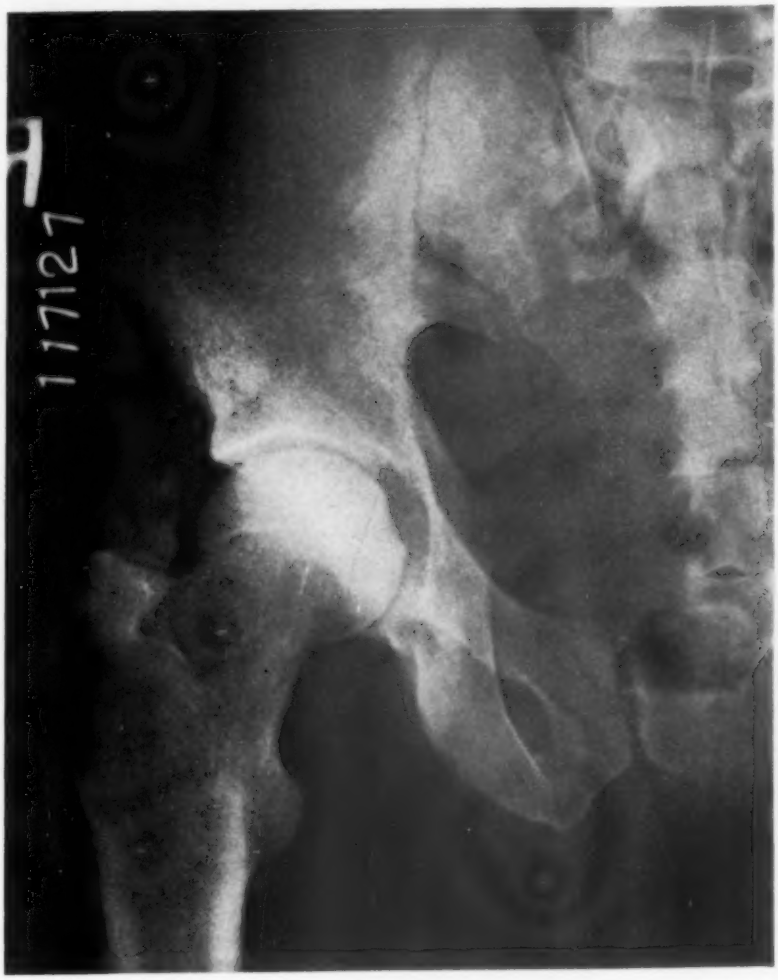

FIG. 3. Roentgenogram of the pelvis.

per liter by the Esbach method. No red blood cells nor hemoglobin were detected in the urine, but a few granular casts and white blood cells were usually present.

The blood contained 5.11 grams of hemoglobin per 100 c.c. (Newcomer) and 1.0 million red blood cells and 5,350 white blood cells per cubic mm. Of the latter, 73 per cent were neutrophiles, 1 per cent eosinophiles, and 26 per cent lymphocytes. The blood Wassermann test was negative. The results of the various blood chemical determinations are shown in chart 1. As will be noted, there was marked azotemia and, although the serum inorganic phosphorus was greatly increased in amount, there was approximately a normal concentration of serum calcium.

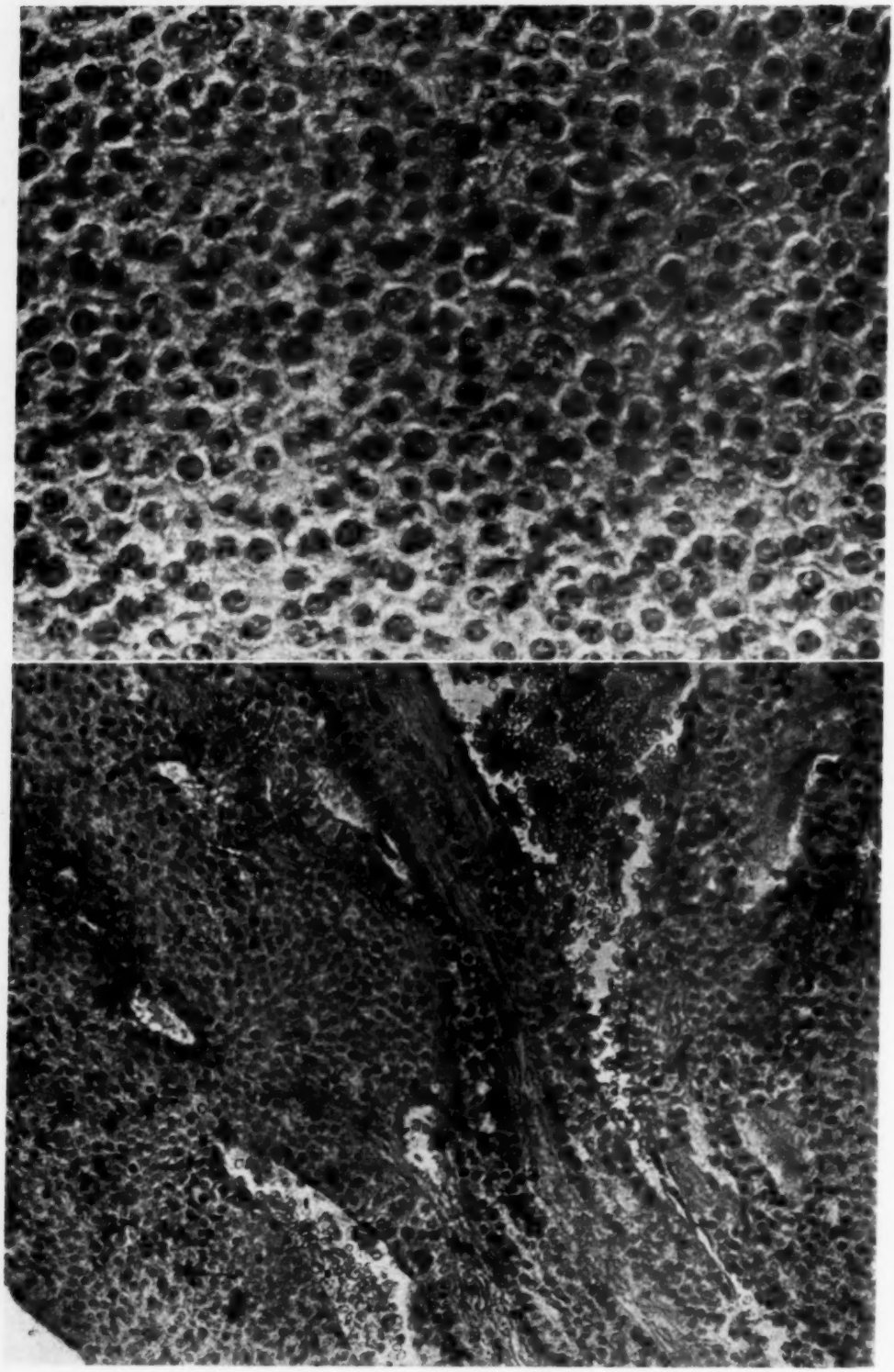

FIG. 4. Sections of the parathyroid.

Calcium and phosphorus balance studies were not satisfactory owing to the inability of the patient to coöperate. However, in the 24 hour test period, immediately following a 48 hour interval during which the patient ingested a diet of low calcium and phosphorus content, the patient ingested no more than 589 mg. of calcium and 1003 mg. of phosphorus and excreted 172 mg. of calcium and 802 mg. of phosphorus in the urine. Roentgenograms (figures 1, 2 and 3) of the skull, pelvis, spine, long bones and hands revealed a generalized osteoporosis but no evidence of cyst formation. The skull had a diffuse, granular appearance with innumerable areas of

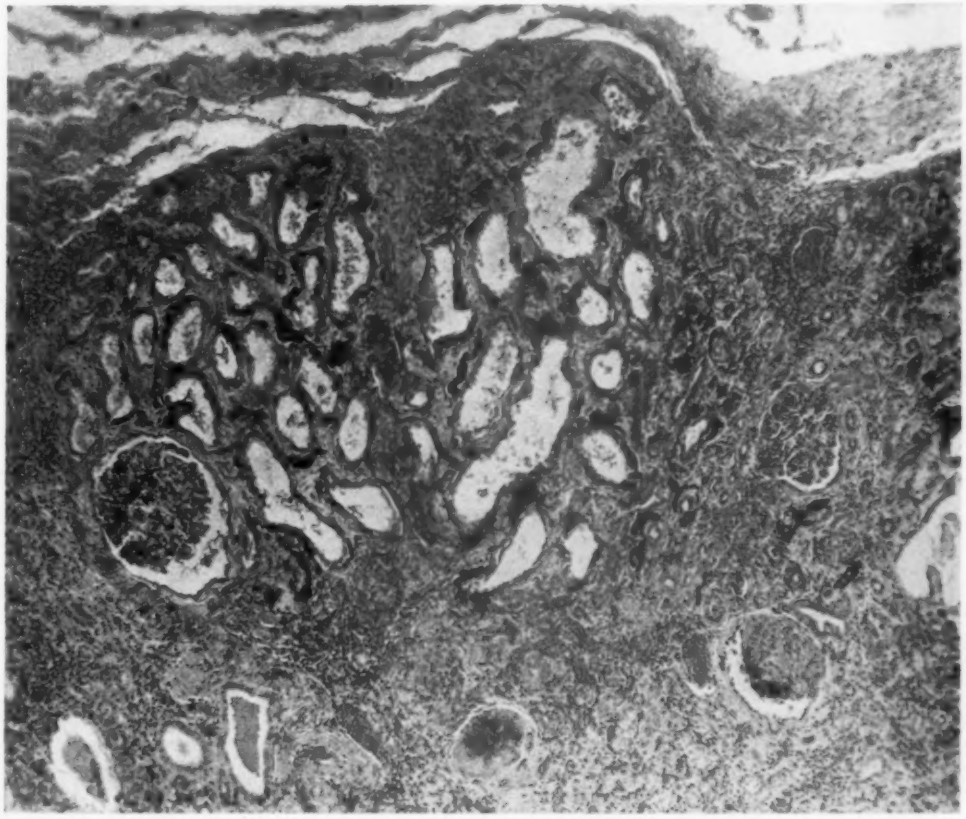

FIG. 5. Section of the kidney.

lessened density. There were localized areas of calcium density in the soft tissues of the terminal phalanx of all fingers and the thumb of the left hand, about the middle joint of the right index finger, and in the tip of the right little finger. There were similar shadows in the regions of the right elbow, right shoulder, and right hip joints. Roentgenograms of the chest, kidney regions, and the mandible to include the mass mentioned above revealed no extraneous shadows of calcium density.

On September 15, 1938, the mass on the tip of the left index finger was incised and a small amount of milky, thick, white fluid was obtained. No calcified nor solid material was present. On September 17, 1938 similar material was aspirated from the bulbous mass about the second joint of the right index finger. Chemical analysis of the fluid showed that it contained 62.55 per cent water and 28.24 per cent tricalcium

phosphate; 7.79 per cent was insoluble in acid and was thought to be protein; and 1.39 per cent was not identified.

The patient died on October 15, 1938. During the 93 day period of observation, nausea, weakness, and generalized pains were progressive. The clinical diagnosis was renal osteitis fibrosa cystica, or hyperparathyroidism secondary to renal disease.

Postmortem examination revealed marked overgrowth of one parathyroid gland,* very small kidneys, generalized osteitis fibrosa, multiple areas of calcification in various organs, generalized arteriosclerosis, coronary arteriosclerosis, myocardial

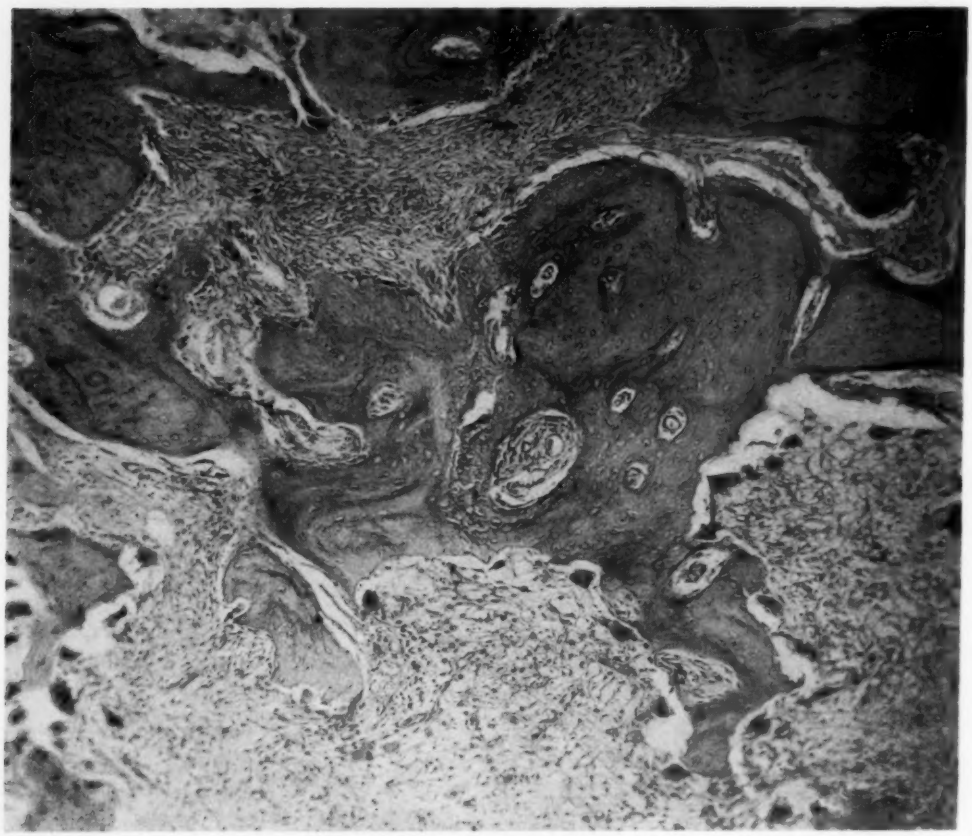

FIG. 6. Section of the skull.

scarring, cardiac hypertrophy and dilatation, lobular pneumonia, passive congestion of the liver, chronic cystitis, hyperplasia of the prostate gland, multiple cysts of the capsule of the spleen, and a cyst of the brain. Examination of the mass anterior to the right ear and of the hands was not permitted. Pertinent gross and microscopic observations follow.

The parathyroid gland measured 5 by 2½ by 2 cm. and contained an area of cystic degeneration in the center. It was composed of masses of closely packed cells separated by wide bands of connective tissue (figure 4). The nuclei occupied the

* A careful search in the neighborhood of the thyroid gland, in the thyroid capsule, and in the upper mediastinum revealed two small masses which were thought to be the other parathyroid glands but were later found to be normal lymph glands.

greater portion of the cells, varied moderately in size, and contained a fine chromatin network, one or more dark blotches of chromatin, and a nucleolus. The cytoplasm of most cells was pale and vesicular but was definitely pink in others. There were numerous blood sinuses around which the cells were lined up in a single row resembling epithelial cells. We believe that the cells anatomically are midway between chief and "wasserhelle" in type. A few scattered, small "wasserhelle" cells were seen but no oxyphil cells could be found.

Each kidney weighed 108 grams and was pale and firm. The capsule stripped away with great difficulty. A cut section revealed the absence of architectural pattern and in many areas it was difficult to detect a line of demarcation between the pyramids and cortex. The cortex was only 3 mm. in thickness. The renal pelves and ureters were normal. Sections of the kidneys (figure 5) showed the surfaces to be pitted and the capsules to be thickened and hyalinized. The glomeruli were greatly reduced in number and were surrounded by atrophic and widely dilated tubules. Collections of glomeruli and tubules were separated from each other by wide areas of scar tissue in which there was evidence of chronic inflammation. There was increased vascularity but the vessel walls were not greatly thickened. Diffuse areas of calcification were conspicuous and numerous throughout the interstitial tissue. Many glomeruli were hyalinized and several showed adhesions between the tuft and capsule. One crescent formation was seen. Many tubules were greatly dilated and some of them contained colloid-like material. A few tubular epithelial cells contained brown pigment and a great many of them contained calcium. The deposits of calcium were very conspicuous both in and about the tubular epithelium and in the interstitial tissue.

The bones of the skull were markedly thickened and the two tables were widely separated by a spongy, reddish-gray, granular tissue. The cortex of the femora and clavicles was normal in appearance. The acromioclavicular joints were very loose owing to the softening of adjacent bone. Sections from the skull (figure 6), clavicles, vertebrae and femora revealed extensive areas of fibrosis between the spicules of bone, many osteoblasts, and numerous osteoclasts. No cysts were seen.

Areas of calcium deposition were prominent in the lungs, brain, pancreas, pineal body, and splenic artery. Arteriosclerosis was moderate but definite.

The cyst of the brain was small, surrounded by edema, and had no definite lining.

Discussion

We base our diagnosis of primary renal disease and secondary hyperparathyroidism on: severe renal insufficiency, probably of long duration in view of the history of albuminuria and pain in the loins; increased serum inorganic phosphorus; normal serum calcium; acidosis; calcium deposits about the joints; sclerosis of the peripheral arteries; widespread osteitis fibrosa. As noted above, these features also fulfill the requirements for a clinical diagnosis of renal osteitis fibrosa cystica. Dr. Fuller Albright of the Massachusetts General Hospital, Boston, has reviewed the case and agrees with our diagnosis.

In view of the fact that only one parathyroid gland was found, we cannot successfully contradict anyone who wishes to call this a case of primary hyperparathyroidism or one of coincidental primary hyperparathyroidism and chronic nephritis. Identification of the parathyroid lesion as that of secondary hyperplasia or that of neoplasia (adenoma) would be decisive but the histological pattern of the gland is not sufficiently characteristic [6, 10] to warrant an unequivocal decision.

As Castleman and Mallory [10] intimate and this case demonstrates, primary hyperparathyroidism resulting in renal damage and primary renal disease resulting in hyperparathyroidism may so closely resemble each other in their respective end stages as to be indistinguishable either clinically or at postmortem examination. As a rule, in the former condition one finds enlargement of only one parathyroid gland unless the disease is due to hypertrophy, in which case the diagnosis is clear from the parathyroid histology whereas, in the latter condition, one would expect enlargement of all four parathyroid glands. The differential diagnosis in our case is difficult because only one gland was found.

Summary

A case of probable hyperparathyroidism with calcinosis and secondary to chronic renal disease is reported. Certain difficulties in the differential diagnosis between this condition and primary hyperparathyroidism with severe renal damage are pointed out.

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REPORT OF A CASE OF BENIGN GASTRIC POLYP PRODUCING A GASTROGENIC DIARRHEA *

By Gordon J. Culver, M.D., Walter Westinghouse, M.D., and E. C. Koenig, M.D., F.A.C.P., *Buffalo, New York*

Benign tumors of the stomach constitute a relatively small portion of gastric lesions. According to the figures of Eusterman and Balfour they represent only 0.6 per cent of all gastric lesions seen at the Mayo Clinic. Mayo Clinic statistics show that the average age of occurrence of benign gastric lesions is 46. Twenty-six per cent occur in the body of the stomach and 69 per cent occur in the pyloric or prepyloric regions. Benign gastric lesions include leiomyomata, fibromata, lipomata, hemangiomata and adenomata. The leiomyoma is the most frequent benign gastric lesion and this usually is polypoid in structure and resembles somewhat submucous fibroid as seen in the uterus. The adenomata are usually multiple.

The most common symptoms of benign lesions in the stomach include dyspepsia, diarrhea, anemia and hematemesis. Nausea and vomiting may occur but are uncommon. The diagnosis is not easy. At the Mayo Clinic a roentgenologic diagnosis was made in 92.6 per cent of the cases. The diagnosis of a benign gastric lesion can hardly be made clinically. The rarity of the lesion and the vague, variable symptomatology are the chief obstacles to clinical diagnosis. Probably the combination of roentgenologic studies and gastroscopic examination followed by surgical exploration is the most accurate and logical method of establishing a diagnosis.

With careful fluoroscopic examination the percentage of correct roentgenologic diagnoses should be high. This is particularly true of pedunculated growths. These are usually freely movable in the lumen of the stomach, and the pedicle is quite easily distinguishable. There is absence of infiltration or rigidity of the surrounding gastric wall, and the growth itself does not usually show areas of ulceration as seen in malignant lesions. In benign growths involving the wall of the stomach, which are not pedunculated, the diagnosis is extremely difficult and unreliable and usually a roentgenologic diagnosis of a malignant lesion is made. Fortunately, however, the greater percentage of benign growths are pedunculated. Multiple polypi in the stomach give characteristic roentgenologic findings but are rarely seen.

Of course, if a benign gastric lesion can be visualized gastroscopically, this is an extremely valuable aid in establishing a diagnosis.

Surgical exploration plus pathologic examination of the specimen is certainly the absolute method of final diagnosis. Because of the frequency of malignant changes in benign gastric lesion surgical exploration and removal of the tumor should not be delayed.

Because chronic diarrhea is such a prominent symptom in gastric polypi it seemed worth while to include at this time a short outline of etiological factors which produce diarrhea in adults so we might more easily see how diarrhea of gastric origin fits into the scheme of other chronic diarrheas.

* Received for publication March 12, 1941.

Outline of etiologic factors which produce diarrhea:

1. Ingesta, including food and drug poisonings.
2. General toxic conditions, as sepsis, toxic goiter, Addison's disease, and Bright's disease.
3. Deficiency diseases, as pellagra and sprue.
4. Secondary circulatory disturbances producing chronic passive congestion of the gastrointestinal tract.
5. Psychic disturbances.
6. Organic disease of the gastrointestinal tract.

   A. Organic disease above the colon.
      1. Gastrogenic
      2. Pancreatogenic
      3. Enterogenic

   B. Organic disease of the colon.

Gastrogenic diarrhea was first described by Oppler in 1896. Eusterman and Balfour state that a gastrogenic diarrhea is the commonest type of chronic diarrhea in adults. They also state that chronic diarrhea is one of the commonest disturbances seen in achlorhydria. We realize that this information differs from other accepted theories on the subject and offer it chiefly because the case we are presenting showed these findings. Alvarez has shown that any condition which favors rapid emptying of the stomach may produce a diarrhea. This occurs because the rapid increase in bulk in the upper small bowel stimulates peristaltic activity which in turn may reflexly cause an increased number of bowel movements. Probably most cases of gastrogenic diarrhea are a result of rapid emptying of the stomach. We know that foreign bodies in the stomach are often associated with a diarrhea. This is probably the result of increased irritability of the stomach by stimulation from the foreign body, with resulting increase in peristaltic activity and more rapid emptying of the stomach. A polyp extending into the gastric lumen might well act the same as a foreign body and thus explain the diarrhea so commonly associated with gastric polypi.

Case Report

Mrs. H. A., a 35-year-old Greek dressmaker, was first seen August 10, 1940. Since May of 1939 the patient had had a persistent diarrhea with three to six stools during the day and two to four stools during the night. Stools were always watery and occasionally contained mucus. Once she passed bright red blood with her stool. Her appetite remained excellent. She had a few attacks of nausea and emesis. Except for occasional crampy abdominal pain no other symptoms had been present. Following eating, diarrhea was apt to increase. The eating of meat in particular increased her diarrhea. The patient had lost 30 pounds since the onset of the illness. Nothing in her past history had any bearing on her present complaint.

On physical examination the patient showed evidence of moderate weight loss. Otherwise, nothing of importance was noted.

Laboratory findings: Urine was negative. Red blood cell count was 3,410,000, hemoglobin 68 per cent, white blood cell count was 9,150; the differential count was normal. Urea nitrogen, glucose, sodium chloride and carbon dioxide combining power were normal. Wassermann reaction was negative. Stools were positive for occult blood on three occasions, but negative for parasites and ova.

Roentgenologic findings: Stomach with barium showed a smooth polypoid structure extending from the greater curvature at about its midpoint into the lumen of the

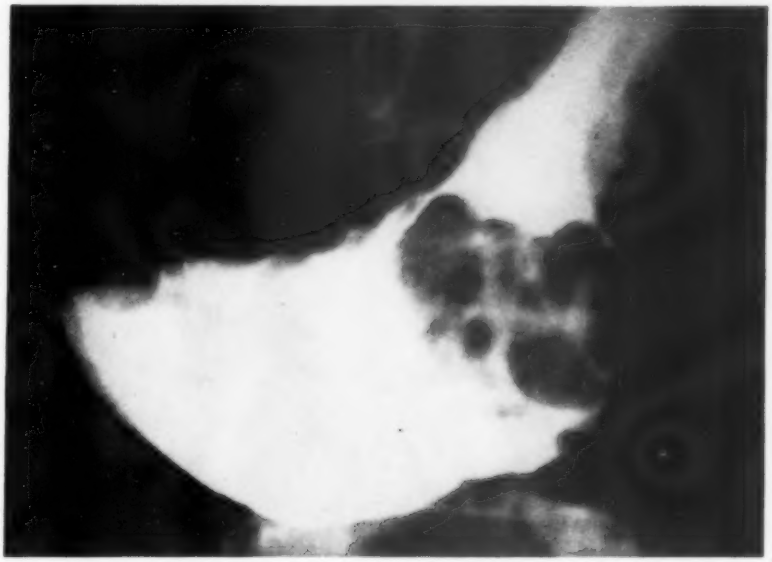

FIG. 1. Roentgenogram showing polypoid filling defect outlined with barium.

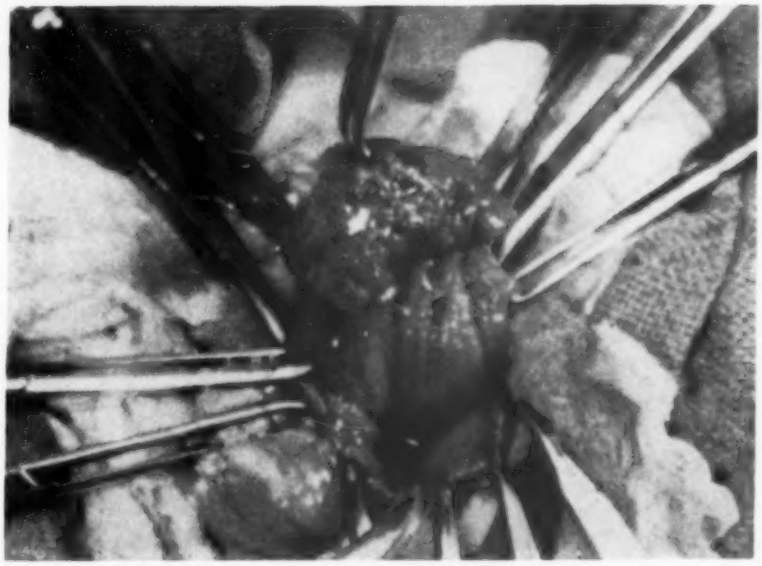

FIG. 2. Surgical field at time of operation showing polyp attached to gastric mucosa. Polyp and attached wall have been brought out through incision in the anterior gastric wall.

stomach. The polyp was almost egg-sized and was freely movable in the lumen of the stomach except at its point of attachment along the greater curvature. Otherwise, the stomach was not unusual in appearance. The duodenal cap filled out well. At

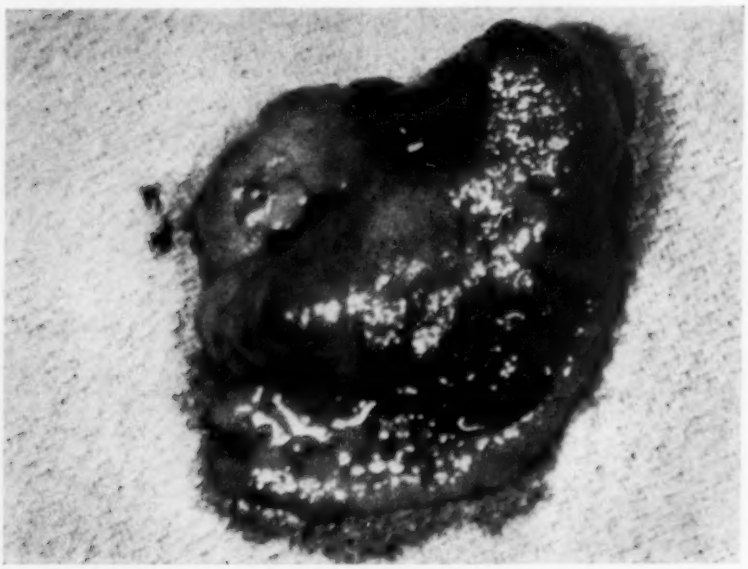

FIG. 3. The excised polyp.

FIG. 4. Photomicrograph of section from the excised polyp.

the end of five hours there was a slight trace of barium in the stomach partially outlining the polyp. Except for the gastric findings the gastrointestinal tract was normal. The colon did not show any pathology. Roentgenologic interpretation: solitary benign polyp of the stomach arising from the greater curvature.

Sigmoidoscopic examination was negative.

Gastroscopic examination: Just above the angulus on the greater curvature aspect there was a tumor mass bulging into the lumen of the stomach. It was redder in color than the surrounding mucosa. The surface was somewhat irregular. The upper portion of the tumor could not be seen. The mucosa of the remainder of the stomach showed marked atrophic gastritis.

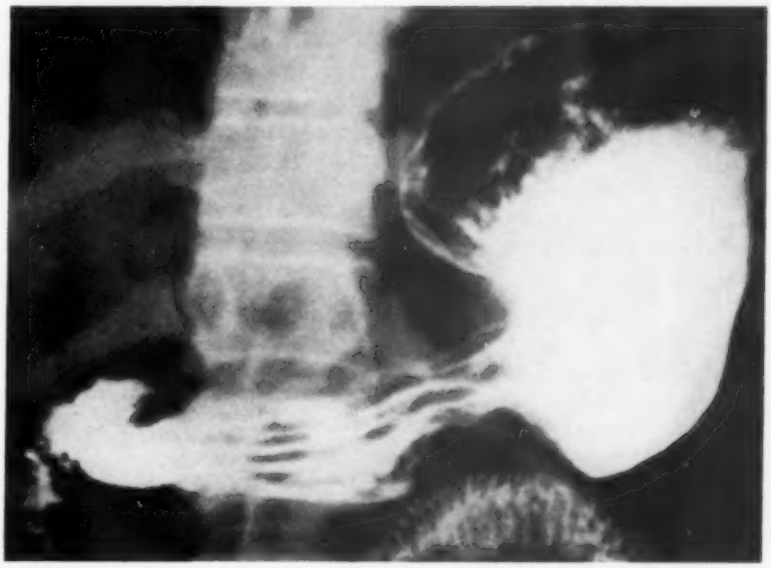

FIG. 5. Roentgenogram of stomach postoperatively showing smooth notching of greater curvature at site of surgical removal of the polyp.

Gastroscopic impression was "polypoid tumor mass on the greater curvature of the stomach. The nature of this tumor cannot be positively ascertained but would favor Grade I carcinoma."

Surgical findings: On September 29, 1940, the polyp was excised from the posterior stomach wall and the wall of stomach repaired.

Pathological findings: (Gross) Papilloma about 15 grams in weight measuring 5 by 4 by 2 cm. Microscopically it was a papillary adenoma of the stomach with marked chronic inflammatory changes throughout the stalk with considerable ulcerations on the surface. There was no evidence of malignancy.

Course: Postoperatively the patient's course was uneventful except for a mild cystitis which rapidly disappeared. Her diarrhea subsided and bowel habits were about normal at the time of discharge on October 26, 1940. On October 25, 1940 the stomach was reëxamined roentgenologically. Except for a smooth notching of the greater curvature at the point of resection of the tumor nothing unusual was demonstrated. The stomach was freely movable. On October 26, 1940 gastric analysis showed an absence of free hydrochloric acid.

Discussion

This case presented a problem which in the first place would obviously be classified as a gastrointestinal disorder and secondly one in which we would expect to find the pathologic lesion located in the lower gastrointestinal tract rather than in the stomach. Cases presenting chronic diarrhea may very well have pathologic changes of the nature found here as the only initiating factor in the symptomatology and a careful analysis and study of the entire gastrointestinal system is of extreme importance.

We believe that the presence of the polyp in this woman's stomach and the marked atrophic gastritis and achlorhydria associated with it were the initiating factors in the marked diarrhea which she experienced. The patient stated that she was unable to eat any meat because of the marked diarrhea which it precipitated, and we assume that protein substances not acted upon by the gastric juices acted as an irritating factor and tended to increase peristalsis which in turn caused rapid emptying of the stomach. The polyp acting as a foreign body likewise tended to increase the activity of the stomach.

In a case report by Weitzen [5] in the New York State Journal in January 1940, on the presence of a bezoar, the symptomatology was somewhat analogous to that noted in this case. In his case there was found in the stomach a ball of ingested thread, present for a long period of time and accompanied by diarrhea and chronic gastritis. There was a tremendous appetite with weight loss. All symptoms disappeared after removal of the bezoar.

In the case we have presented, following surgical removal of the lesion there was a complete cessation of symptoms. The patient received no medication.

The only treatment for benign gastric lesions is early surgical removal. The reasons for this are obvious:

It is necessary in order to relieve the patient's symptoms, and these lesions tend to undergo malignant changes.

We cannot emphasize too strongly the importance of complete gastrointestinal studies in cases of chronic diarrhea of obscure etiology. A negative barium enema does not mean that there is not some organic lesion in the gastrointestinal tract which is responsible for a chronic diarrhea.

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POST-RADIATION PANMYELOPHTHISIS CLINICALLY SIMULATING AGRANULOCYTOSIS *

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Among writers on hematology and roentgen therapy it has become customary to list, often with considerable qualification, excessive radiation as a potential cause of agranulocytosis.[1, 2, 3] It was called to the attention of a member of this hospital staff who had cited such statements in a recent publication [4] that examples of this type of reaction had been rarely if ever reported. Consequently, it was with extreme interest that we observed the course of the following case.

Case Report

A 43 year-old-white woman was admitted to the Wisconsin General Hospital on September 7, 1939. Her chief complaint was of a mass in the abdomen. This was first noted during June of 1939. Other significant symptoms were anorexia, constipation, dyspnea on slight exertion, and progressive weight loss (60 pounds since December 1938). Her occupation was that of a housewife, and she admitted no exposure to benzene, coal tar derivatives, or drugs of any type. She had had occasional headaches which she called migraine. Physical examination revealed pallor; enlarged, very firm lymph nodes in the cervical, axillary and inguinal regions; pleural effusion on the left; enlarged liver and spleen and multiple firm, fixed intra-abdominal masses. There was a slight intermittent fever, with a maximum of 99.8° F. Hemoglobin was 12.2 grams. There were 4,740,000 red blood cells, 9,400 white blood cells, with 91 per cent neutrophiles, 7 per cent lymphocytes, and 2 per cent monocytes. The Wassermann reaction was negative. Blood sugar, non-protein nitrogen, gastric acidity, urinalysis and the appearance of the upper gastrointestinal tract and colon on roentgen-ray study were within normal limits. A roentgenogram of the chest confirmed the findings of pleural effusion and demonstrated enlargement of the mediastinal lymph nodes and partial atelectasis of the left lower lobe. An electrocardiogram suggested toxic myocardial involvement. In a biopsied inguinal lymph node small round cells with scanty cytoplasm and large vesicular nuclei completely overgrew the gland, destroying the architecture and invading the capsule (figure 1).

A diagnosis of lymphosarcoma was made and roentgen therapy instituted. Exposing one fourth of the body surface at a time, a dose of 50-r † was twice given to each area in turn, and then 200-r was given to each of three abdominal preaortic node areas and to the splenic area. All radiation was given between September 15, 1939 and September 29, 1939, no more than one area being treated each day. Daily counts showed some fluctuation, but on September 27 the white blood cell level was still 6,900; on September 29, however, it fell abruptly to 950, and continued to fall thereafter.

Intensive therapy with large doses of pentnucleotide, intramuscular liver extract, and yellow bone marrow concentrate was promptly started, and three 500 c.c. transfusions given, but without apparent benefit. On October 3 there were 325 leukocytes,

* Received for publication January 20, 1941.

From the Department of Medicine, Wisconsin General Hospital and the University of Wisconsin Medical School.

† Factors:

0.5 mm. copper and 1.0 mm. aluminum filters were used throughout.
For general body irradiation, FSD was 60 cm., at 160 kv. and 7.5 milliamps.
For abdominal nodes, FSD was 50 cm., at 175 kv. and 15 milliamps.

with 2.5 per cent neutrophiles, 22.5 per cent eosinophiles, 50 per cent small and 2 per cent large lymphocytes, 12 per cent young lymphocytic forms, 0.5 per cent monocytes, and 10.5 per cent cells which appeared to be of the lymphoid group but were so pathologically altered or primitive in form as not to be definitely classifiable. Platelets were estimated from the smear as a high normal in number, and the red count (4,735,000) and hemoglobin (14.7 gm.) were well within normal limits. The total leukocyte count steadily decreased, reaching a final low on October 7 of 75, of which 94 per cent were lymphocytes, 4 per cent blasts, and 2 per cent primitive or unclassified

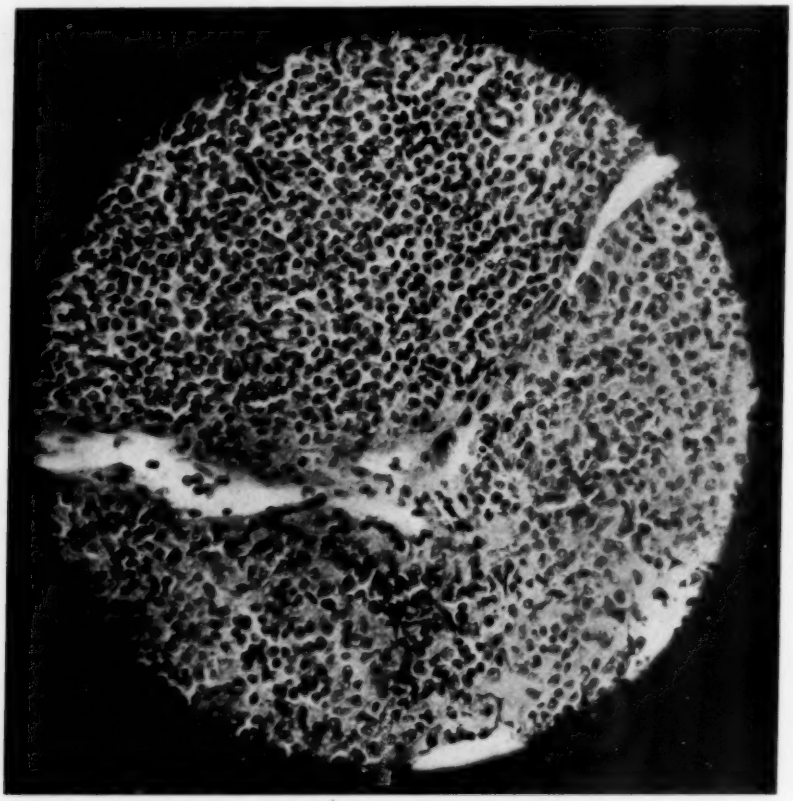

FIG. 1. Photomicrograph of lymph node obtained by biopsy, showing lymphosarcomatous change. (× 440).

cells. Unfortunately, no hemoglobin nor red cell determinations were performed after October 4, but on this date, with the white count 450, hemoglobin was 12.2 grams, the same value as that on admission. On October 7 the red cells still appeared normal in the smears, but there was an apparent decrease in the number of platelets. On October 8, 23 days after beginning radiation therapy, the patient died.

A sternal biopsy on October 5 showed 0.2 per cent neutrophiles, 4 per cent eosinophiles, 63.4 per cent small, 5 per cent intermediate, and 6 per cent young lymphocytes, 0.6 per cent large young cells, 6 per cent unclassified cells, 1.4 per cent primitive cells, 3 per cent pathological cells, and 10.4 per cent plasma cells. Thirty normoblasts, one primitive red cell, and numerous polychromatophilic erythrocytes were seen during a count of 500 white cells.

The patient was remarkably free of symptoms and almost euphoric at times during this period. Anorexia, nausea and some pain at the site of pentnucleotide injections were the only complaints until the day preceding death, when a sense of substernal constriction, slight dyspnea, and a cough productive of a little sputum appeared. Between October 3 and October 8 she had a remittent fever varying between 99.8 and 102.8° F. There were never any oropharyngeal lesions, but at the sites of all intramuscular injections painful, indurated, dusky red to black areas appeared, and very few petechiae were seen. A faint scleral icterus was present the morning of October

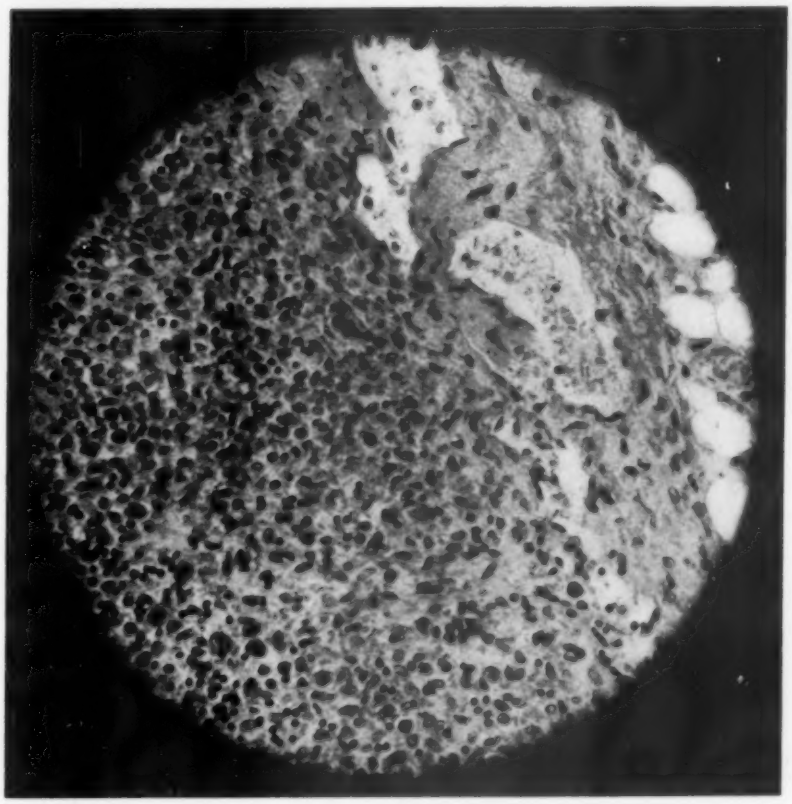

FIG. 2. Photomicrograph of lymph node removed at autopsy, showing decrease in lymphoid elements, with pyknosis and fragmentation of nuclei and phagocytosis of degenerating cells. Some early fibrotic change is also visible. (× 440).

8, and within a few hours a rapidly deepening generalized jaundice was seen. An icterus index performed on blood obtained a few minutes post mortem was 45.

Nembutal (totaling 4½ grains and last given approximately four weeks before exitus), acetyl salicylic acid (gr. v on September 8), nicotinic acid (last dose September 26), ephedrine sulphate (gr. ⅜ q.i.d. from September 27 to October 5), and one dose each of morphine sulphate (gr. ⅛) and scopolamine (gr. 1/200) were the medications received during her hospitalization, in addition to the drugs given in an effort to combat the progressive granulocytopenia. None of these drugs is to our knowledge considered a cause of agranulocytosis.

Necropsy: Gross examination * showed an obese, generally icteric female with purplish black swollen areas of necrosis on the arms, thighs, and buttocks. The left lung was almost completely atelectatic, with 1700 c.c. of icteric fluid occupying the remainder of the left pleural cavity. The right lung was crepitant throughout, and free of gross lesions except at the base where a 5 cm. area of hemorrhage was present. The mediastinal nodes formed a large, firm, irregular mass, dry and mottled pinkish gray on section. The heart was small (270 gm.), flabby, and showed early brown atrophy. There was slight coronary and aortic atherosclerosis. The spleen weighed

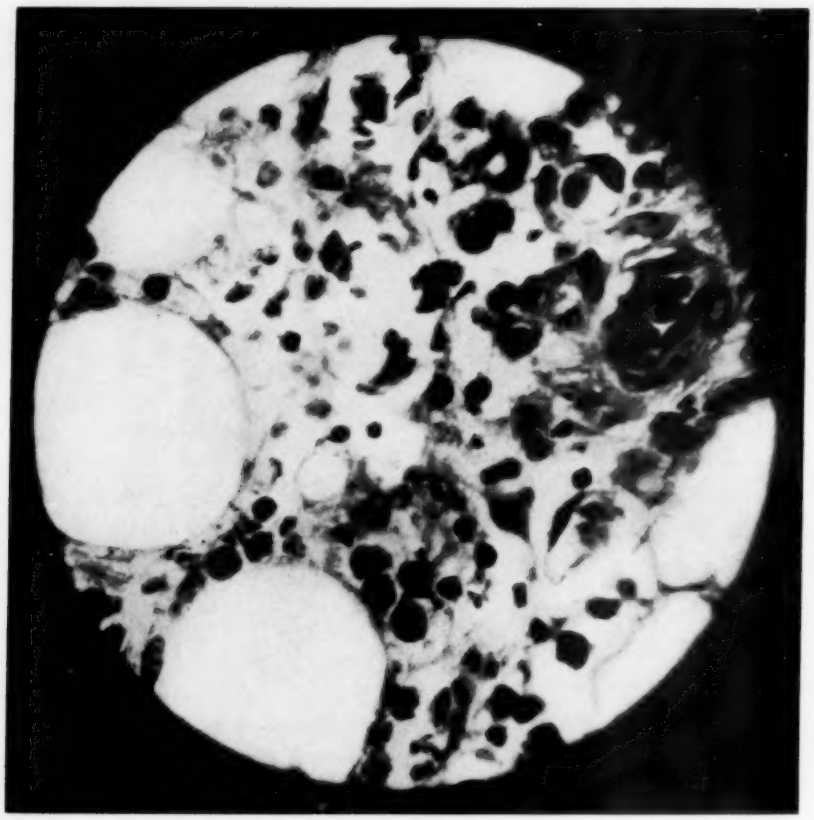

FIG. 3. Vertebral marrow (× 950) obtained at autopsy. Loss of cellularity with relative increase in numbers of lymphocytes and plasma cells, general degeneration of hematopoietic elements, and some fibrinous exudate may be seen.

650 gm., was dark purple in color, and quite firm in consistency. There were firm matted masses of lymph nodes in the retroperitoneal and pelvic areas, in the mesentery, and about the stomach and pancreas. The bone marrow was dark red.

Microscopic examination: The lymph nodes showed loss of normal architecture and atrophy of lymphoid elements, with much fibrosis, many phagocytes filled with lipoid material, and many endothelial cells, as well as small areas of hemorrhage (figure 2). The discolored areas of the right lung showed extensive hemorrhage containing many bacterial colonies; similar clumps of bacteria were present in the areas of sub-

* Performed by Dr. Leonard Long.

cutaneous necrosis. There was chronic passive congestion of the lungs, liver, and spleen. The spleen also showed loss of architecture, atrophy of the lymphoid and increase in the endothelial elements, considerable fibrosis and endarteritis, areas of hemorrhage and hyaline necrosis in the pulp, and a number of eosinophiles. Bone marrow from the ribs, sternum, vertebrae, and femur all showed a great many disintegrating cells, many pyknotic and fragmented nuclei, some hyaline necrosis, disintegrating scanty megakaryocytes, a network of fibrinous material in many areas, areas of hemorrhage, and some beginning fibrosis, especially about the blood vessels. A considerable number of large reticuloendothelial cells were seen, as were a few lymphocytes and an occasional plasma cell. Erythropoietic and myelopoietic centers were few and relatively inactive, many showing distinct necrosis (figure 3). The few fairly normal appearing areas were mainly in the femoral marrow, where there also appeared to be a slight increase in the number of eosinophiles. Postmortem blood culture showed *Staphylococcus aureus*. Other findings were not remarkable.

It is probable that the relatively longer life span and greater resistant qualities of the red cells masked the destructive changes in their formative elements until the time of death, and that these changes would have become apparent had the patient lived longer. Similar factors may have conditioned the relative eosinophilia in the earlier counts. Clinically there was nothing to suggest that this was not a true agranulocytosis, although the laboratory finding of a suggestively low percentage of normoblasts in the sternal biopsy specimen might have been considered of possible significance. Consequently, the postmortem finding of marrow damage so extensive and severe as to amount almost to a complete aplasia of all the hematopoietic elements was unexpected, and suggested that an examination of the literature in regard to this point might prove of interest.

In spite of a careful, thorough search, no clear cut, fully reported cases of pure agranulocytosis secondary to radiation could be found, although cases reported by Lovett,[5] Fiessinger and associates,[6] and in the review of Bock and Wiede [7] are quoted as such, e.g., by Rosenthal.[3] Lovett, in a report on a case of agranulocytosis, says in passing, of another case: "In a patient operated on for carcinoma of the prostate and treated afterward with roentgen-rays and radium, the white count fell to 200 cells per cubic millimeter, with only 4 per cent of polymorphonuclear leukocytes. He developed angina of a type similar to that of our patient before death." No further details are given, however, so it is not possible to be sure just what process may have occurred. Fiessinger's case was a woman of 63 who, when first seen with a condition diagnosed as cholecystitis, had a leukocyte count of 13,200, of which 67.5 per cent were lymphocytes and 28 per cent neutrophiles. Nine months later, following a "grippal coryza," a large spleen was discovered. Roentgen-ray therapy to the spleen was commenced, although the authors state that they made no pretense of diagnosing the cause of the splenomegaly. Four treatments of "34 filtres par 5/10 de millimetre d'aluminum" * were given at weekly intervals. There was no application over the long bones. Six days after the fourth treatment slight fever and extreme fatigue were noted. Blood count showed red blood cells 4.1, white blood cells 330, neutrophiles 0.3 per cent, eosinophiles 2 per cent, basophiles 1 per cent, large monocytes 14 per cent, medium-sized monocytes 75 per cent, lymphocytes 15 per cent, and neutrophilic myelocytes 2 per cent (total 109.3 per

* No unit of dosage was given by the author.

cent?). Intramuscular injections of milk were given, with a prompt rise to 10,000 white blood cells with 79 per cent neutrophiles. The authors state that "this is without doubt a syndrome of agranulocytosis"; indeed, it may well have been. But the preëxisting splenomegaly and relative neutropenia, without satisfactory explanation, leave something to be desired regarding the diagnosis and possible etiology. The review of Bock and Wiede refers to two cases of their own, one an assistant physician and one a nurse in a radium station, who were found to have, respectively, white counts of 5,100 with 34 per cent granulocytes and 6000 with 46 per cent granulocytes; and in a review of the literature regarding agranulocytosis, to the cases of Siegels [8] as cited by Flaskamp.[9] Little further information regarding their own cases is given, though they were said to be slowly improving at the time of publication, but on the basis of their description it would be difficult to classify them as true agranulocytosis. Siegels' report is a study of the peripheral blood in 15 patients carefully followed for 10 days to two years after radiation for various pelvic disorders, and in nine workers in his clinic. In only one of his 280 post-radiation counts did the total white count fall below 3300, or the neutrophile count below 2000, and in this case a count of 2200 white blood cells with 1936 neutrophiles was found 10 days after treatment for an inoperable carcinoma. Simultaneous hemoglobin value was 43 per cent and red count 3,020,000. He records two other absolute neutrophile counts between 2000 and 2800, and eight between 2800 and 3000. It seems rather doubtful that these cases can be considered as agranulocytosis.

Not only were no definite cases of agranulocytosis found, but reported experimental observations on the hematological effects of radiant energy lend little support to the idea that there is any selective action on the granulocytic system. Instead, such effects seem to be differentiated purely on a quantitative and chronological basis, and to be modified in their reflection in the peripheral blood picture by the relative length of life of the adult form of each cell type. Further, the changes seem to be purely destructive. Nothing was encountered to suggest that a stem cell or myeloblastic hyperplasia without maturation, such as is described in many cases of agranulocytosis, is ever seen as a result of radiation. The resemblance to the group of agranulocytoses described as having hypoplastic marrow, among which Schultz' original case [10] apparently belongs, is somewhat greater, at least as regards the granulocytic series. In such cases, however, Darling, Parker, and Jackson [11] found only marked depletion in numbers of the granulocytic stem cells, with a total absence of more mature forms. There was replacement by lymphocytes and myriads of plasma cells, but nothing in the nature of the acutely degenerative changes which are seen after exposure to roentgen-rays. Custer [12] did find degeneration and necrosis in his most acute cases, but even here they were limited almost entirely to the granulocytic cells.

From the many excellent studies on blood diseases due to exposure to roentgen-rays, e.g., Brinnitzer [13] and Flaskamp,[9] and on the blood and marrow findings after therapeutic radiation, e.g., Minot and Spurling,[14] Selling and Osgood,[15] and Casati, a composite idea of the resultant changes may be postulated. This would suggest that a given amount of radiation will affect all cell types, but in different degrees, lymphoid tissue being most susceptible, erythropoietic least, the granulocyte and megakaryocyte series intermediate, and that the latent periods vary. There seems to be first a rise and then a fall in the

absolute lymphocyte count, overlapped by a similar change starting a little later and proceeding more slowly in the neutrophile group. If the damage be severe enough the erythrocyte count may later fall; but often the longer life span of the circulating red cells and the lower sensitivity of the erythropoietic elements are adequate to prevent any peripheral manifestation of the changes in the red series. Monocytes, eosinophiles, and basophiles seem to resemble the neutrophiles in their reaction, but with a slightly lower degree of susceptibility; reports in regard to them are few and conflicting. Findings with respect to platelets vary also, but the majority opinion seems to be that they follow an intermediate course between that of the red and white cells.

Of interest in this respect is another case recently admitted on the pediatric service in this hospital. A boy 10 years old had been diagnosed as having acute leukemia, and over a period of four weeks before admission had received radiation totaling 2635-r over the splenic, cervical, mediastinal and axillary areas. Additional radiation of 700-r (100-r at each of seven treatments in a period of eight days) over the splenic area was given here. The patient died one month after the last roentgen-ray treatment. Sternal, vertebral and rib marrow obtained at necropsy showed an extensive and active fibrotic process with almost complete absence of hematopoietic elements.

Summary

1. A case of post-radiation panmyelophthisis which clinically simulated agranulocytosis has been presented.

2. A search of the literature failed to reveal any clear cut, fully reported cases of agranulocytosis due to radiation.

3. A review of the published reports of the effects of radiation on hematopoietic tissues suggests that the occasional appearance of what seems to be severe uncomplicated neutropenia due to roentgen-rays is actually a manifestation of a generalized marrow damage. The peripheral reflection of this damage has been modified by the interplay of the varying life spans and by the rates of reaction of the various cell types, rather than by any isolated effect on the neutrophilic series, either of a destructive or of a maturation inhibiting type.

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EDITORIAL

SULFADIAZINE

Less than eight years ago Domagk published his initial report on the striking effects of the brick-red dye prontosil in experimental hemolytic streptococcal infections in mice. Shortly thereafter it was found that a relatively simple chemical compound, sulfanilamide, or para-amino-benzene-sulfonamide, was the active constituent of prontosil. These discoveries marked the dawn of a new era in the chemotherapy of bacterial infections. As a result a stupendous amount of experimental work has been carried out and the medical literature has been flooded with articles on the effects of the various sulfonamides in the treatment of infectious diseases. Many new compounds have been synthesized, tested out in the laboratory, and then administered to patients. We have seen in succession sulfanilamide, neo-prontosil, sulfapyridine, sulfathiazole, and finally sulfadiazine added to our therapeutic armamentarium. With such a variety of drugs to choose from the chief problem that confronts the physician today is the selection of the most effective drug for the treatment of a given infection.

Sulfanilamide was found to be highly active against infections due to the beta hemolytic streptococcus, meningococcus, gonococcus and Welch bacillus, but relatively ineffective against pneumococcal infections. Unfortunately this drug gave rise to a number of toxic manifestations in many patients. One of the more serious toxic effects was acute hemolytic anemia which developed during the first week of therapy in about 3 per cent of all patients receiving sulfanilamide. Fatal granulocytopenia was encountered occasionally in patients who had taken the drug for over two weeks. Hepatitis (occasionally acute yellow atrophy), peripheral neuritis, and psychosis were other infrequent but serious toxic effects. In addition to these serious toxic effects which are relatively rare, minor complaints such as headache, dizziness, nausea, anorexia, or mental confusion were common to the majority of patients treated with sulfanilamide. Drug fever and dermatitis were by no means rare. Cyanosis, due either to methemoglobinemia or to a colored by-product of sulfanilamide, was more alarming to the family than to the physician since it was rarely of serious import. Acidosis with a fall in the carbon dioxide combining power of the blood was frequently a disturbing feature until it was found that this complication could be prevented by administering sodium bicarbonate with each dose of sulfanilamide. Because of these multiple toxic and unpleasant side-effects, sulfanilamide has largely given way today to the less toxic sulfadiazine as the drug of choice for the treatment of hemolytic streptococcal, meningococcal, and Welch bacillary infections. Sulfanilamide still maintains a definite though limited position among the sulfonamide drugs. In therapeutic doses sulfanilamide has not caused renal damage (gross hematuria or anuria) such as occurs in a small

but significant proportion of patients treated with sulfapyridine, sulfathiazole, or sulfadiazine. Therefore sulfanilamide is still the drug of choice for the treatment of patients with hemolytic streptococcal infections complicated by hemorrhagic nephritis or other serious renal disorders. Furthermore, powdered sulfanilamide, because of its greater solubility and diffusibility, has been found superior to its three more modern derivatives for local implantation in the treatment of traumatic wounds or infections in the peritoneal cavity.

Sulfapyridine was first employed extensively in the treatment of pneumococcal pneumonia in the winter of 1938–1939. The results were dramatic and the case fatality rate in lobar pneumonia was reduced by nearly two-thirds. Here at last was a drug that proved to be highly effective against the pneumococcus. Unfortunately, however, several difficulties arose in connection with the administration of sulfapyridine. Because of its low solubility, absorption from the gastrointestinal tract was often slow and many hours were required to obtain an effective blood level of the drug. This obstacle was surmounted by the administration of an initial intravenous injection of 4.0 grams of the relatively soluble sodium salt of sulfapyridine, followed by the oral administration of 1.0 gram of sulfapyridine every four hours as a maintenance dose. The worst feature of sulfapyridine therapy was the extremely high incidence of nausea and vomiting (of central origin) following the administration of the drug either orally or intravenously. At times dehydration from severe vomiting necessitated the intravenous administration of saline and glucose. Patients were frequently heard to say that they would prefer to take their chances with the disease rather than the cure. It became obvious that, although sulfapyridine was an extremely potent antipneumococcal agent, it was a long way from an ideal solution of the pneumonia problem.

In 1939 sulfathiazole succeeded sulfapyridine as the drug of choice for the treatment of pneumococcal infections. This compound was more soluble than sulfapyridine and hence more readily absorbed. The incidence of nausea and vomiting from sulfathiazole was much lower than that from sulfapyridine. Sulfathiazole is more rapidly excreted than sulfapyridine and it is, therefore, difficult to maintain an effective blood level of the drug. Furthermore, sulfathiazole has subsequently proved to be the most toxic of the four sulfonamide compounds in general use today, giving rise to a higher incidence of serious toxic effects such as drug fever, dermatitis, hepatitis, granulocytopenia, hemolytic anemia, and renal complications. Rich [1] has very recently demonstrated periarteritis nodosa-like lesions in the tissues of patients who have been treated with sulfathiazole. Evidences of renal damage in the form of gross hematuria as a result of the precipitation of drug

[1] RICH, A. R.: The rôle of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy, Bull. Johns Hopkins Hosp., 1942, lxxi, 123–140.

crystals in the kidneys or oliguria due to direct toxic damage to the renal tubules have been noted in a large enough proportion of patients treated with sulfapyridine or sulfathiazole to necessitate careful observation of the urine and fluid balance in all patients receiving these drugs.

Finally in 1940 sulfadiazine was introduced in the hope that it would surpass sulfathiazole as an antipneumococcal agent. Two years later we find that sulfadiazine has stood the test of time as the drug of choice for the treatment of pneumococcal lobar pneumonia. Sulfadiazine is fairly well absorbed from the intestinal tract. It is less rapidly conjugated and more slowly excreted than sulfathiazole, and is just as effective. Most important of all, sulfadiazine is far less toxic than sulfapyridine or sulfathiazole. In a recent review of a large number of cases treated with one or another of the four drugs, Long [2] found the incidence of serious toxic effects such as drug fever, dermatitis, acute hemolytic anemia, granulocytopenia, renal complications, hepatitis, peripheral neuritis, and psychosis to be as follows: sulfathiazole 18.6 per cent, sulfapyridine 15.9 per cent, sulfanilamide 11.9 per cent, and sulfadiazine 6.5 per cent. Thus sulfadiazine is only about one third as toxic as sulfathiazole. Acute hemolytic anemia from sulfadiazine must be extremely rare.

Elsewhere in this issue Finland and his associates [3] advocate sulfadiazine as the drug of choice for the treatment of hemolytic streptococcal, pneumococcal, meningococcal, and Friedländer bacillary infections. They recommend sulfadiazine in all acute pulmonary infections and acute meningitides; also in gonococcal or staphylococcal infections where prolonged therapy is desirable. This report is in general accord with the attitude of other authorities in the field, notably Long, Dowling, Flippin, Trevett, and Wood. The reasons for this viewpoint are twofold: (1) equal or superior efficacy of sulfadiazine in the treatment of the infections mentioned, and (2) low toxicity. Sulfadiazine is not the ultimate answer to the problem of chemotherapy for bacterial infections, but it is by far the best of the sulfonamide compounds available at the present time. Its shortcomings are apparent: (1) low solubility with relatively slow absorption, a difficulty which may be circumvented, as in the case of sulfapyridine or sulfathiazole, by an initial intravenous injection of the sodium salt of sulfadiazine; (2) toxicity, in particular drug fever, dermatitis, and renal damage; and (3) cost (the price of sulfadiazine is still considerably higher than that of any of the other three compounds). These disadvantages are more than outweighed by the special merits of the drug. Patients receiving sulfadiazine rarely complain of unpleasant symptoms such as headache, dizziness, malaise, nausea or vomiting. The valency of the drug is much wider than that of any one of its predecessors. True, sulfathiazole and sulfapyridine are still

[2] Long, P. H.: Personal communication to the author.

[3] Finland, M., Peterson, O. L., and Goodwin, R. A.: Sulfadiazine: further clinical studies of its efficacy and toxic effects in 460 patients, Ann. Int. Med., 1942, xvii, 920–934.

regarded as being superior to sulfadiazine for treatment of acute gonococcal infections and certain infections of the urinary tract. Yet sulfadiazine already gives promise of supplanting the other sulfonamides as the drug of choice in many of these genito-urinary infections. Further investigation is necessary before final conclusions can be drawn.

All in all, sulfadiazine stands out as the most effective and least toxic of the sulfonamides available to the physician today. At the moment it is the king of the sulfonamides.

W. H. B.

REVIEWS

Text Book of Clinical Parasitology. By DAVID L. BELDING, M.D. 888 pages; 25 × 16 cm. 1942. D. Appleton-Century Co., New York. Price, $8.50.

This book contains an excellent comprehensive survey of the entire field of human parasitology, including the arthropod vectors of disease as well as the parasitic protozoa and helminths. It is more comprehensive than the title "Text Book" might suggest. Although attention is given primarily to the commoner parasites of greatest practical importance, a large number of rare or occasional parasites receive brief but adequate consideration.

The author has followed a uniform procedure in discussing each parasite: history, geographical distribution, biological characteristics, life cycle, pathogenesis, symptomatology, immunity, diagnosis, prognosis, treatment, and prevention. This is an advantage from the standpoint of clarity and ease in finding desired information, although it results in considerable repetition. He has stressed the clinical features more than the average text book, but the consideration of the zoölogical phases of the subject is the more authoritative.

The most distinctive feature of the book is the large number of tables (44) and diagrams which are very useful both from the standpoint of teaching and of finding essential information quickly. The book is profusely illustrated. There are many simple line drawings so arranged as to facilitate the identification or differentiation of related species. The geographical distribution of the important parasites and the life cycles are graphically demonstrated.

The book closes with a useful section on technical methods and on parasiticidal and anthelmintic drugs.

The work is well up to date, and is documented with numerous references. It is a valuable contribution and is recommended to those interested in the subject.

P. W. C.

Modern Drug Encyclopedia and Therapeutic Guide. Second Edition. By JACOB GUTMAN, M.D., Phar.D., F.A.C.P. 1644 pages; 24 × 16 cm. 1941. New Modern Drugs, New York. Price, $10.00.

The second edition of this very useful reference book is cordially welcomed by the many admirers who were familiar with the first edition published in 1934. The author remarks that since 1934 many remarkable advances as well as many vital changes have been made in drug therapy which are of paramount importance to the medical profession.

Accurate and concise information is presented concerning all the popular non-pharmacopeial preparations including biologicals, allergens, potent drugs and endocrine products with the name of the manufacturer, brief description, action and uses, how supplied, dosage and administration.

The material is satisfactorily arranged, the reference is readily made, and those who are accustomed to having the volume on their desks or on a nearby shelf would miss it sadly if removed.

A quarterly supplement helps one keep up to date.

T. P. S.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Sulfanilamide and Related Compounds in General Practice. Second Edition. By WESLEY W. SPINK, M.D., F.A.C.P. 374 pages; 21 × 14.5 cm. 1942. Year Book Publishers, Inc., Chicago. Price, $3.00.

Diseases of the Liver, Gallbladder and Bile Ducts. By S. S. LICHTMAN, M.D., F.A.C.P. 906 pages; 24 × 15.5 cm. 1942. Lea and Febiger, Philadelphia. Price, $11.00.

Changes in the Knee Joint at Various Ages. By GRANVILLE A. BENNETT, M.C., HANS WAINE, M.D., and WALTER BAUER, M.C. 97 pages of text plus 31 plates; 26 × 17.5 cm. 1942. The Commonwealth Fund, New York. Price, $2.50.

Hemolytic Syndromes. By WILLIAM DAMESHEK, M.D., TIBOR J. GREENWALT, M.D., RUSSELL J. TAT, M.D., and CAMILLE DREYFUS, M.D. 41 pages; 31 × 24 cm. 1942. Privately printed. (A reprint of an exhibit sponsored by the New England Medical Center, Boston. Presented at the 1942 Convention of the American Medical Association, Atlantic City, June 1942.) Price, $1.50.

Thoughts of a Psychiatrist on the War and After. By WILLIAM ALANSON WHITE, M.D. 28 pages; 26 × 18 cm. 1942. The William Alanson White Psychiatric Foundation, Inc., Washington, D. C. (Republished essay—originally copyrighted by Paul E. Hoeber in 1919.) Price, $1.50.

Osler's Principles and Practice of Medicine. Fourteenth Edition. By HENRY A. CHRISTIAN, M.D., F.A.C.P. 1500 pages; 25 × 17 cm. 1942. D. Appleton-Century Co., New York. Price, $9.50.

Blood Substitutes and Blood Transfusion. Edited by STUART MUDD, M.A., M.D., and WILLIAM THALHIMER, M.D. Seventy Collaborating Investigators. 407 pages; 24.5 × 16 cm. 1942. Charles C. Thomas, Springfield, Illinois. Price, $5.00.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Previously reported in these columns were the names of 973 members of the American College of Physicians serving in the armed forces of their country. Herewith are reported the names of 92 additional members, bringing the grand total to 1,065.

Elsewhere in these columns appears an age analysis of members of our College. Considering the fact that the average age of all members of the College, Masters, Fellows and Associates, is 48.9 years, the number, 1,065, on active duty from a total membership of approximately 4,800, is indeed impressive.

David I. Abramson
Wardner D. Ayer

Orpheus J. Bizzozero
Oscar Blitz
Allen G. Brailey
Russell S. Bray
Osborne A. Brines
Norton S. Brown
Philip W. Brown
L. Clair Burket

Horace B. Cates
Olin B. Chamberlain
Richard E. Ching
Morgan Cutts
Casimir J. Czarnecki

John S. Davis, Jr.
William F. Dobyns
Charles H. Drenckhahn
Early D. DuBois
Garfield G. Duncan

Edwin G. Faber
Henry Felson
Arthur N. Ferguson
John W. Ferree
Maurice P. Foley
John V. Fopeano
Meyer Friedenson
Louis Friedfeld

John F. Giering
Wilton R. Glenney
Douglas M. Gordon
George A. Gray
Harold J. Gunderson
Ramsdell Gurney

Everett E. Hammonds
Ben R. Heninger
Meredith B. Hesdorffer
Edward D. Hoedemaker
Arthur A. Holbrook
A. Gerson Hollander
Roy H. Holmes
Benjamin Horn
Lyman H. Hoyt

Alfred P. Ingegno

Robert R. Janjigian
William N. Jenkins
Thomas A. Johnson

Samuel R. Kaufman
Henry B. Kirkland
Elmer A. Kleefield

Charles A. Landshof
Aleksei A. Leonidoff
John B. Levan

Willard Machle
A. Seldon Mann
John K. Martin
William S. McCann
Charles A. McKendree
J. Stuart McQuiston
Jonathan C. Meakins
Oliver J. Menard
George W. Millett
John H. Mills
John B. Morey
Frank R. Mount

Algot R. Nelson
Arthur D. Nichol

George C. Owen

Felix R. Park
Julius R. Pearson
L. Lewis Pennock
A. Robert Peskin

Herbert W. Rathe
Harold F. Robertson
William W. Rucks, Jr.

Leo V. Schneider
Maurice A. Schnitker
Fred F. Senerchia, Jr.
Edward V. Sexton
Kenneth K. Sherwood
J. Shirley Sweeney

Ivan Thompson

David Ulmar

William von Stein

Joseph Weinstein
Joseph F. Whinery
Thomas J. White
Henry M. Winans
Andrew C. Woofter
Arthur T. Wyatt

Lloyd B. Young

John I. Zarit

Average of A. C. P. Members 48.9 Years

A recent analysis of the ages of the members of the American College of Physicians, as of October 15, 1942, reveals that the average age of the 4 Masters is 74.3 years; the average age of the 3,705 Fellows is 51.3 years; and the average age of the 1,110 Associates is 40.9 years. The average age for the entire membership of Masters, Fellows, and Associates is 48.9 years.

The following table gives the distribution in various age groups. In the highest age group there is 1 Fellow 94 years of age, 1 Fellow and 1 Associate 89 years of age, 1 Fellow 88 years of age, 1 Fellow 85 years of age, and 1 Master, 15 Fellows, and 2 Associates between 80 and 84.

Associates in the higher age groups constitute a group who became Associates in 1926 by virtue of being members of the American Congress on Internal Medicine, and who, by the terms of the merger of the Congress with the College, were not required to present credentials for advancement to Fellowship.

Age Group	90–94	85–90	80–84	75–79	70–74	65–69	60–64	55–59	50–54	45–49	40–44	35–39	30–34	26–29	Total
Associates		1	2	11	12	24	22	29	49	113	199	373	258	17	1,110
Fellows	1	3	15	47	119	261	380	462	680	662	624	384	67		3,705
Masters			1		2	1									4
	1	4	18	58	133	286	402	491	729	775	823	757	325	17	4,819

New Life Member

Dr. James Murray Flynn, F.A.C.P., Rochester, N. Y., became a Life Member of the American College of Physicians on October 10, 1942.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Francis R. Dieuaide, F.A.C.P., Boston, Mass.—"Civilian Health in Wartime";
Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C.—"Abnormal Arterial Tension";
Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio—"Selected Reprints from the Department of Physiology of Western Reserve University School of Medicine," two bound volumes.

Reprints

Dr. George E. Baker, F.A.C.P., Casper, Wyo.—1 reprint;
J. Edward Berk (Associate), Captain, (MC), U. S. Army—3 reprints;
Dr. J. Bailey Carter, F.A.C.P., Chicago, Ill.—10 reprints;
Dr. William Herbert Ordway, F.A.C.P., Mt. McGregor, N. Y.—1 reprint;
George C. Owen (Associate), Major, (MC), U. S. Army—1 reprint;
Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.—1 reprint;
Dr. William Kendrick Purks, F.A.C.P., Vicksburg, Miss.—2 reprints;
Herbert W. Rathe, F.A.C.P., Captain, (MC), U. S. Army—1 reprint;
Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C.—17 reprints;
Dr. Paul F. Whitaker, F.A.C.P., Kinston, N. C.—5 reprints;
Dr. Burton L. Zohman, F.A.C.P., Brooklyn, N. Y.—1 reprint.

The Department of Pharmacology of the George Washington University School of Medicine, Washington, D. C., contributed a bound volume entitled, "Studies from the School of Medicine, The George Washington University, 1941–1942," as a gift to the College Library.

Luncheon Meeting Held by Virginia Members, A. C. P.

Dr. J. Edwin Wood, Jr., F.A.C.P., Acting Governor of the College for Virginia, reports a luncheon meeting of the Virginia members in Roanoke in early October. Following the luncheon a business session was held. Dr. R. Finley Gayle, F.A.C.P., Richmond, presided as Regional President. Dr. Ernest G. Scott, F.A.C.P., Lynchburg, was made Regional President for the coming year. Dr. Alexander F. Robertson, Jr., F.A.C.P., Staunton, was reëlected Secretary-Treasurer. The meeting was highly successful with a very good attendance. It was determined not to hold a regular autumn State meeting of the College members as in previous years, due to transportation difficulties and the inability of many physicians to attend.

Michigan State Medical Society Will Hold 1943 Annual Meeting

The Executive Committee of the Council of the Michigan State Medical Society has determined to continue its annual meetings and will hold its 78th such meeting at the Statler Hotel, Detroit, during the week of September 20, 1943. Monday and Tuesday of the week will be given to the meeting of the House of Delegates, of which Dr. P. L. Ledwidge, F.A.C.P., Detroit, is the Speaker. Wednesday, Thursday, and Friday will be given to a streamlined program of general assemblies.

At the recent meeting of the Society, Dr. H. H. Cummings, Ann Arbor, was installed as President and Dr. C. R. Keyport, Grayling, was named President-Elect.

Dr. Frederick T. Zimmerman (Associate) is now associated with Columbia University College of Physicians and Surgeons, New York, N. Y., his specialty being

experimental neurology. Dr. Zimmerman is Research Assistant in the Department of Neurology and Instructor in Neurology and Psychiatry in the University Extension Division. He is also Junior Assistant Neurologist at the New York Neurological Institute.

On September 29, 1942, Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., spoke on "Dietary Deficiencies Exaggerated by Therapeutic Diets" at the meeting of the Lackawanna County Medical Society in Scranton and on October 3 he spoke on "Nutrition in Industry" at a meeting of the Pennsylvania Railroad Surgeons in Pittsburgh. On October 22 Dr. Kelly conducted a symposium on "Medical Aspects of Parodontosis" and an exhibit on dietary deficiency diseases at a meeting of the Fifth District Dental Society in Harrisburg.

Among those who will speak at the Friday Afternoon Lecture Series for 1942–1943, sponsored by the New York Academy of Medicine, are:

January 29, 1943—Dr. S. Bernard Wortis, F.A.C.P., New York, N. Y.—"Modern Treatment of the Psychoses";

February 19, 1943—Dr. Robert L. Levy, F.A.C.P., New York, N. Y.—"Clinical Types of Coronary Insufficiency and Their Recognition";

February 26, 1943—Dr. Maurice Bruger (Associate), New York, N. Y.—"Recent Advances in the Clinical Interpretation of Laboratory Data";

March 19, 1943—Harold J. Harris (Associate), Lieutenant Commander, (MC), U. S. Navy—"Brucellosis: Diagnosis, Differential Diagnosis and Treatment."

Dr. Robert K. Dixon, F.A.C.P., Denver, Colo., has been appointed a member of the Colorado State Board of Medical Examiners.

Dr. R. Garfield Snyder, F.A.C.P., New York, N. Y., discussed "Recent Advances in the Treatment of Arthritis" at a recent meeting of the Bridgeport (Conn.) Medical Society.

Dr. Paul A. O'Leary, F.A.C.P., Rochester, spoke on "Technic for Intravenous and Intramuscular Administration of Antisyphilitic Remedies" at the annual session of the Southern Minnesota Medical Association, September 28, 1942.

Dr. Alexander H. Stewart, F.A.C.P., Harrisburg, has been appointed Secretary of the Pennsylvania Board of Health. Dr. Stewart served as Deputy Secretary from 1939 to 1941 and since 1941 had been serving as Acting Secretary.

The Association of American Medical Colleges held its fifty-third annual meeting in Louisville, Ky., October 26–28, 1942. Among those who spoke were:

Dr. Hugh R. Leavell, F.A.C.P., Louisville, Ky.—"Coördinating Program of Health, Hospital and Medical School in a Municipal University";

Dr. E. Cowles Andrus, F.A.C.P., Baltimore, Md.—"Medical Research in Wartime";

Dr. S. Spafford Ackerly, F.A.C.P., Louisville, Ky.—"The Teaching of Psychiatry to Undergraduate Medical Students";

Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn.—"Teaching of Nutrition."

During August Dr. George E. Burch, F.A.C.P., Instructor in Medicine at Tulane University School of Medicine, New Orleans, conducted a graduate course in internal medicine and cardiovascular diseases at the Hospital Santo Tomás, Panama City, R. P.

John L. Kantor, F.A.C.P., Colonel, (MC), U. S. Army, discussed "Digestive Symptoms in the Tuberculous and Their Management" at a joint meeting of the University of Colorado School of Medicine and the National Jewish Hospital in Denver, Colo., November 2, 1942.

Dr. George E. Wakerlin, F.A.C.P., Professor and Head of the Department of Physiology of the University of Illinois College of Medicine, Chicago, Ill., is directing research in experimental renal hypertension at the University. The John and Mary R. Markle Foundation has authorized a grant-in-aid of $7,000 over a two-year period for the support of this research.

The Association of Life Insurance Medical Directors of America held its fifty-third annual meeting in Philadelphia, Pa., October 21–22, 1942. Among the speakers were:

Eugen G. Reinartz, F.A.C.P., Colonel, (MC), U. S. Army—"Effect of Flight on Man";

Dr. Frank N. Wilson, F.A.C.P., Ann Arbor, Mich.—"The Precordial Electrocardiogram";

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa.—"Military Neuropsychiatric Disabilities and Their Treatment."

The Los Angeles Heart Association held its twelfth annual symposium on cardiovascular disease in Los Angeles, Calif., November 12–13, 1942. Among the speakers were:

Dr. John M. Askey, F.A.C.P., Los Angeles, Calif.—"The General Practitioner and His Choice of a Digitalis Preparation";

Dr. Morris H. Nathanson, F.A.C.P., Los Angeles, Calif.—"Practical Use of Adrenalin and Related Compounds in Cardiovascular Disease";

Dr. Harold J. Hoxie (Associate), Los Angeles, Calif.—"Rupture and Other Complications of Myocardial Infarction."

Dr. Oscar O. Miller, F.A.C.P., Louisville, Ky., was named one of the vice presidents of the Kentucky State Medical Association at its annual meeting in Louisville, October 1, 1942.

The Wayne County (Mich.) Medical Society, the Detroit District Dental Society, the Detroit Physiological Society, the Detroit Pediatric Society, and the Engineering Society of Detroit have arranged a series of lectures on nutrition in medicine, dentistry, and industry. The first lecture in this series was presented on October 12, by Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala., who spoke on "Recent Advances in Vitamin Research." On November 19, 1942, Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill., spoke on "What's Wrong with America's Diet?"

Dr. S. Bernard Wortis, F.A.C.P., Associate Professor of Neurology at the New York University College of Medicine, has been appointed the first Lucius N. Littauer Professor of Psychiatry and Visiting Neuropsychiatrist in charge of the psychiatric division of Bellevue Hospital. The appointment of Dr. Wortis became effective October 1, 1942. This professorship has been named in honor of the philanthropist who last year established a fund of nearly $250,000 for "research in psychiatry, neurology and related fields, in order to increase and diffuse knowledge of the biological and other factors which influence thought and conduct; and thereby to prevent and correct abnormal human behavior through clinical and experimental approaches."

The Oklahoma City Clinical Society held its twelfth annual fall conference October 26–29, 1942. Dr. James E. Paullin, F.A.C.P., President of the College and President-Elect of the American Medical Association, was the guest of honor. Among the guest speakers at the conference were Dr. Sara M. Jordan, F.A.C.P., Boston, Mass.; Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn.; Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala.; and Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.

Dr. Albert E. Russell, F.A.C.P., U. S. Public Health Service, New York, N. Y., spoke on "Problems of Civilian Medical Service in War Times" at a meeting of the Cambria County Medical Society at Johnstown, Pa., October 8, 1942.

Dr. Walter M. Boothby, F.A.C.P., Rochester, Minn., spoke on "Recent Research in the Mayo Aero Medical Unit" and Eugen G. Reinartz, F.A.C.P., Colonel, (MC), U. S. Army, spoke on "Neuropsychiatric Aspects of Aviation Medicine" at the annual meeting of the Aero Medical Association of the United States in Indianapolis, Ind., September 3–5, 1942.

The Association of Military Surgeons held its annual meeting at San Antonio, Tex., November 5–7, 1942. Among the speakers were the following:

James C. Magee, F.A.C.P., Major General, (MC), U. S. Army, The Surgeon General —"An Appraisal of the Medical Department at War";

Dr. Charles M. Griffith, F.A.C.P., Washington, D. C.—"Medical and Hospital Service Experience with Disabled Veterans of World War II";

Charles R. Reynolds, F.A.C.P., Major General, (MC), U. S. Army, Retired, Harrisburg, Pa.—"Medical and Epidemiological Follow-Up of Selective Service Men Rejected for Military Service";

Leonard G. Rowntree, F.A.C.P., Colonel, (MC), U. S. Army—"Selective Service System—Wartime Problems of Selective Service";

Dr. Neil D. Buie, F.A.C.P., Marlin, Tex.—"The Work of the State Medical Association of Texas on Procurement and Assignment Service for Doctors, Dentists and Veterinarians."

The Southern Medical Association held its annual meeting in Richmond, Va., November 10–12, 1942. Among the speakers were:

Henry M. Thomas, Jr., F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—"Peptic Ulcer in the Army";

Dr. Robert Wilson, Jr., F.A.C.P., Charleston, S. C.—"Acute Hemolytic Anemia in Fertilizer Workers: A New Industrial Hazard";

Dr. William Henry Sebrell, Jr., F.A.C.P., U. S. Public Health Service, Bethesda, Md. —"Foods and Their Importance to the War Effort";
Dr. Francis M. Rackemann, F.A.C.P., Boston, Mass.—"The Natural History of Asthma";
Dr. Robert L. McMillan (Associate), Winston-Salem, N. C.—"Ventricular Tachycardia as a Therapeutic Problem in Coronary Thrombosis";
Leon H. Warren (Associate), Major, (MC), U. S. Army—"Patch Tests: Their Practical Applications and Limitations."

On November 11, 1942, Dr. James E. Paullin, F.A.C.P., Atlanta, Ga., President of the American College of Physicians, was the guest speaker at a wartime luncheon sponsored by the Southern Medical Association for the officers of the Association, presidents, presidents-elect, secretaries and editors of state medical associations in the South. Dr. Paullin spoke on "The Value of Medical Organizations in the War Effort."

Dr. Parley Nelson (Associate), Rexburg, has been named President-Elect of the Idaho State Medical Association.

Dr. Italo F. Volini, F.A.C.P., Chicago, Ill., spoke on "The Oral, Intravenous and Intra-Abdominal Uses of Sulfonamides" at a postgraduate conference, October 22, 1942, sponsored by the Illinois State Medical Society in cooperation with the Peoria County Medical Society in Peoria, Ill.

On December 10, 1942, Edgar Erskine Hume, F.A.C.P., Colonel, (MC), U. S. Army, spoke on "War and Medicine" at a lecture for the public sponsored by the New York Academy of Medicine.

Dr. Tom Lowry, F.A.C.P., Professor of Clinical Medicine, has been appointed Dean of the University of Oklahoma School of Medicine, Oklahoma City. Dr. Lowry succeeds Dr. Robert U. Patterson, F.A.C.P., who has been Dean since 1935 and is retiring because of age. Dr. Lowry will serve from November 15, 1942, to July 1, 1943.

Among the speakers at the annual meeting of the Central Society for Clinical Research, held in Chicago, November 6–7, 1942, were:
Dr. Raphael Isaacs, F.A.C.P., Chicago, Ill.—"Effect of Pectin on the Coagulation of Blood in Thrombocytopenic Conditions";
Dr. Edgar A. Hines, Jr., F.A.C.P., Rochester, Minn.—"Experiences with Treatment of Migraine with Potassium Thiocyanate";
Dr. Clifford J. Barborka, F.A.C.P., and Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill. —"Influence of a Diet Deficient in the Vitamin B Complex on the Work Output of Trained Subjects: Experimental Procedure";
Dr. Frederick Steigmann (Associate), Chicago, Ill.—"Causes of the Drop of the Plasma Vitamin A Level in Liver Diseases."

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., spoke on "Epidemic Disease in the United States Army" at a joint scientific meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia, November 11, 1942.

The following Fellows of the American College of Physicians are Diplomates of the American Board of Psychiatry and Neurology though they are not so listed in our 1941 Directory:

Dr. Larue Depew Carter, Indianapolis, Ind.
Dr. Andrew C. Gillis, Baltimore, Md.
Dr. Mark Alexander Griffin, Asheville, N. C.
Dr. William Ray Griffin, Asheville, N. C.
Dr. Samuel Bernard Hadden, Philadelphia, Pa.
Arthur Orr Hecker, Major, (MC), U. S. Army
Dr. Cullen Ward Irish, Los Angeles, Calif.
Dr. Henry Ashley Luce, Detroit, Mich.
Dr. Andrew Ignatius Rosenberger, Milwaukee, Wis.
James Newton Williams, Lieutenant Commander, (MC), U. S. Navy

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Mellon Institute, Pittsburgh, Pa., is distributing gratis to all interested specialists who request them copies of a publication entitled, "Structure and Antipneumococcic Activity in the Cinchona Series."

Dr. James D. Bruce Now Vice-President Emeritus of the University of Michigan

Dr. James D. Bruce, F.A.C.P., former President of the American College of Physicians, retired October 17, 1942, as Vice-President in Charge of University Relations of the University of Michigan, with the title of "Vice-President Emeritus." Dr. Bruce has been director of postgraduate medicine at the University since 1928, and vice-president since 1931. He graduated from the Detroit College of Medicine in 1896 and first joined the faculty of the University of Michigan as assistant in internal medicine in 1904. In the succeeding years he served as director of internal medicine at the medical school, chief of medical service at the Hospital, chairman of the division of health service and chairman of the division of health service and chairman of the division of extramural service. His organization and direction of post-graduate medical education throughout the State of Michigan is a monument to his leadership and administrative capacity.

SPECIALTIES AND SUB-SPECIALTIES AMONG MEMBERS OF THE AMERICAN COLLEGE OF PHYSICIANS

An analysis of the 1941 Directory of the American College of Physicians, and of the 1942 Supplement thereto, presents the following figures. These specialties and sub-specialties have been designated by the members themselves. It may be reasonable to state that a great many do general internal medicine, though they are primarily interested in certain specific sub-specialties. In the classification, Cardiology might reasonably be added to Diseases of the Chest, for undoubtedly this latter specialty does not indicate tuberculosis alone, but the whole range of diseases of the chest, whereas certain members have used the designation "Cardiology" to differentiate from diseases of the lungs.

Over the years it is apparent that a very few members have drifted away from Internal Medicine to engage in surgical specialties, the number being 12 primary and 21 secondary.

	Primary		Secondary	
INTERNAL MEDICINE		3360		88
Allergy	10		156	
Arthritis	5		72	
Aviation and Military Medicine	11		30	
Cardiology	57		714	
Diseases of the Chest	117		347	
Endocrinology	5		69	
Gastro-enterology	43		317	
Hematology and Blood Diseases	2		33	
Immunology and Preventive Medicine	4		22	
Medical Education and Administration	21		36	
Metabolic Diseases	11		180	
Physical Therapy	—		28	
Research	2		47	
Tropical Medicine	9		26	
Total, sub-specialties		297		2077
TOTAL, INTERNAL MEDICINE		3657		2165
GENERAL MEDICINE		258		18
NEUROLOGY, PSYCHIATRY		217		197
PATHOLOGY, CLINICAL PATHOLOGY		187		132
PEDIATRICS		146		39
RADIOLOGY, ROENTGENOLOGY		102		29
PUBLIC HEALTH, STUDENT HEALTH		62		30
DERMATOLOGY, SYPHILOLOGY		48		51
INDUSTRIAL MEDICINE		16		14
BACTERIOLOGY		12		21
SURGICAL SPECIALTIES		12		12
MISCELLANEOUS				
Anatomy	2		4	
Biological Chemistry	2		3	
Cancer	1		—	
Chemotherapy	—		1	
Histology	—		1	
Legal-cultural Medicine	1		1	
Leprosy	—		1	
Life Insurance Medicine	2		3	
Medical History	—		1	
Nephritis	—		1	
Nutrition	—		5	
Pharmacology	6		3	
Physiology	9		1	
Retired	80		—	
Toxicology	—		3	
Vital Statistics	—		1	
Total, Miscellaneous		103		29
NO SECONDARY SPECIALTY GIVEN				2083
		4820		4820

SPECIAL NOTICES

A Course in Electrocardiographic Interpretation

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at Michael Reese Hospital by Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each week starting Wednesday, February 17, 1943 for 12 weeks from 7:00 to 9:00.

Further information and a copy of the program may be obtained on application to the Cardiovascular Department, Michael Reese Hospital.

PRIZE ANNOUNCEMENT

A prize of $100 is offered by the Menninger Foundation for Psychiatric Education and Research for the best suggestion for a window display in a New York bank presenting the uses and purposes of psychiatry. The window is thirteen feet long, six feet high, and its deepest point about eight feet; it curves so that it is narrower at the ends. It will be seen chiefly by laymen and hence the display should be in the nature of an educational theme, convincingly and graphically presented. It should dramatize the way in which psychiatry can be or is being useful either in the present war emergency or in peace time.

The judges will be Dr. George Stevenson, Director of the National Committee for Mental Hygiene, Mr. Albert Lasker, of Lord and Thomas, and Dr. Lawrence Kubie.

Ideas should be submitted in detail, preferably with drawings or diagrams, directly to Dr. William C. Menninger, Director of The Menninger Foundation, Topeka on or before January 31, 1943.

OBITUARIES

DR. MAURICE LEWISON

Dr. Maurice Lewison, F.A.C.P., died in Chicago of a tumor of the brain on June 17, 1942, at the age of 56. He was born in Worcester, Massachusetts, May 18, 1886, and moved with his family to Chicago when he was 14. Two years later he graduated from Medill High School. In 1906 he received his M.D. degree from Northwestern University Medical School.

He served his internship in Cook County Hospital and in 1920 took postgraduate work in London. Upon completion of his internship he joined the medical faculty of the University of Illinois and taught physical diagnosis and tuberculosis almost to his death. He was a full Professor in the Department of Medicine. He took his work seriously and was most meticulous in attendance. He was a lucid and forceful teacher. He always stressed the important and continually emphasized the value of bedside observation.

Dr. Lewison early became interested in tuberculosis, both from the medical and social aspect. After a long apprenticeship in the dispensaries of the Municipal Tuberculosis Sanitarium he became attending physician in the department of tuberculosis of Cook County Hospital. He was soon appointed Chief of Service and was Consultant at the time of his death.

In 1919 he was appointed attending physician in medicine in Mount Sinai Hospital. Within the walls of this institution Dr. Lewison did his best work and spent the happiest years of his life. His ability, sincerity of purpose, and common sense soon won for him the appreciation of Staff and the Board. He became President of the Medical Staff and at the expiration of his tenth year in office was unanimously elected Honorary President. Until his very death he maintained a deep interest in the hospital and its growth.

Dr. Lewison was a member of the Chicago Medical Society, Illinois Medical Society and the American Medical Association. He held memberships in the Chicago Tuberculosis Society, Chicago Heart Association, the Institute of Medicine and was certified by the American Board of Internal Medicine. He became a Life Member of the American College of Physicians in 1941. He was an able clinician whose counsel was sought frequently by younger colleagues not alone because of his wide experience in medicine, but also his good common sense and warm friendliness. He was senior author of a Manual of Physical Diagnosis.

Dr. Lewison was a member of the Phi Delta Epsilon Medical Fraternity. As a teacher and physician he was deeply interested in the development of the Medical Department of the Hebrew University of Palestine and gave without stint of his time and substance to its cause.

He had a keen civic sense and every appeal for the common weal found in him warm response and whole hearted support. He served on the boards of many charitable institutions of the city.

In his death Chicago sustained a deep loss—the city a good citizen, the medical profession a fine physician, and his many patients a capable healer of a kindly and understanding heart. Mount Sinai Hospital lost a very devoted friend of unusual organizing ability, fine judgment, and deep loyalties.

He is survived by his wife; his son, Edward F. Lewison, a graduate of the University of Chicago and Johns Hopkins Medical School, now on active duty as Captain in the Medical Corps of the United States Army; and a daughter, Ethel Mae, a senior at the University of Chicago.

ISADORE M. TRACE, M.D., F.A.C.P.

DR. H. RAWLE GEYELIN

Dr. H. Rawle Geyelin, F.A.C.P., New York, N. Y., was born in Villanova, Pa., on May 12, 1884, and died on September 7, 1942. He received his A.B. degree from the University of Pennsylvania in 1906 and his M.D. degree from the University of Pennsylvania School of Medicine in 1909. From 1913 to 1916 Dr. Geyelin was Instructor in Clinical Pathology at Columbia University College of Physicians and Surgeons; from 1916 to 1917, an Associate in Clinical Pathology; from 1917 to 1921, an Associate in Medicine, and since 1921, an Assistant Professor of Medicine at this University. From 1912 to 1916 he was Blumenthal Fellow in Medicine at Presbyterian Hospital; from 1915 to 1921, an Assistant Visiting Physician; from 1918 to 1919, Chief of the Medical Clinic of the Vanderbilt Clinic of this Hospital, and since 1921, Associate Attending Physician. Dr. Geyelin served as Consulting Physician from 1923 to 1928; Assistant Visiting Physician from 1928 to 1932 and since 1932 as Associate Attending Physician at Babies Hospital. Since 1929 he was a member of the Medical Board of Doctors Hospital.

Dr. Geyelin was a member of the New York Academy of Medicine, the New York Clinical Society, the Interurban Clinical Club, the Harvey Society, the Medical Society of the State of New York, the American Association for the Advancement of Science, the American Clinical and Climatological Association, the American Institute of Nutrition, the American Society for Clinical Investigation, the Association of American Physicians, and the Society for Experimental Biology and Chemistry. He was a Diplomate of the American Board of International Medicine, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1937.

Dr. Geyelin was the author of many articles which were published in outstanding medical journals.

Dr. Geyelin was one of the outstanding internists and his death is a great loss to the medical profession and to the teaching staff of the College of Physicians and Surgeons.

ASA L. LINCOLN, M.D., F.A.C.P.
Governor for Eastern New York

DR. WILLIAM JOSEPH RYAN

Dr. William Joseph Ryan, F.A.C.P., Pomona, N. Y., was born on December 22, 1889, in Norway, Herkimer County, New York, and died on February 20, 1942. He received his medical degree from the Albany Medical College in 1915 and served his internships and houseship in the Homeopathic Hospital of Albany, the Faxton Hospital of Utica and Metropolitan Hospital of New York City. He was resident physician at the Otisville Municipal Sanatorium for two years; following this appointment he was Director of the Tuberculosis Division of the United States Veterans Bureau in 1920. In 1921 he became Superintendent and Medical Director of the Summit Park Sanatorium. In addition to this he was Director of the Rockland County Chest Clinic, Consultant in Diseases of the Chest at the Nyack, Good Samaritan (Suffern), Rockland State (Orangeburg) and Tuxedo Memorial (Tuxedo Park) Hospitals, and Letchworth Village (Thiells). He was former President of the New York State Association of Superintendents and Boards of Managers of County Tuberculosis Sanatoria; former Chairman, Tuberculosis Sanatorium Conference of Metropolitan New York; Secretary of the Rockland County Medical Society; Vice President of the Eastern Section of the American Trudeau Society; member of the New York Society for Thoracic Surgery, New York State Medical Society, American Medical Association, American Sanatorium Association, National Tuberculosis Association, International Union Against Tuberculosis, American Association of School Physicians and American Public Health Association; Fellow of the American College of Chest Physicians; Fellow of the American College of Physicians since 1937. He served during World War I with the rank of First Lieutenant. He was the author of many published articles.

Dr. Ryan made a very enviable record in the various posts which he held and was one of the outstanding chest men of this state. His untimely death was a real loss to the medical profession.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York

DR. LEON EARL KING

Dr. Leon Earl King (Associate) of Hot Springs, Arkansas died July 10, 1942. Dr. King was born in Russia May 23, 1908, and came to this country in his early teens. He was graduated from the High School of Little Rock, Arkansas, with the highest honors and after receiving his Bachelor of Science degree in medicine from the University of Arkansas in 1929, received the Doctor of Medicine degree from the University of Arkansas in 1931. He served internships at Jewish Hospital in St. Louis, Missouri, and the Leo N. Levi Hospital in Hot Springs, Arkansas.

Dr. King practiced for ten years in Hot Springs, where he was a member in good standing of the Garland County Medical Society, the Arkansas Medi-

cal Society, the American Medical Association and the American College of Physical Therapy. He became an Associate of the American College of Physicians in 1938. He was on the staff of the Leo N. Levi Hospital and St. Joseph's Hospital.

Although he lived sixty miles away, Dr. King took time to instruct some of the students at the University of Arkansas Medical School.

In many ways Dr. King was an unusual person. He was a student of languages, particularly French, Russian, German and Latin, and in spite of his foreign birth and early training he had mastered the American language so that he could speak without accent.

Professionally he was particularly interested in arthritis and had published several articles on this disease, the last one appearing in the April, 1942 issue of the *Arkansas Medical Journal.* He was held in high esteem by all his confreres in Hot Springs and his untimely death by a skull trauma has removed one of the ablest practitioners from the profession.

OLIVER C. MELSON, M.D., F.A.C.P.,
Governor for Arkansas

DR. RAYMOND A. RAMSEY

Dr. Raymond A. Ramsey, of Columbus, Ohio, died August 19, 1942. He was born in 1886 and received his medical degree at Western Reserve University School of Medicine in 1912. He became Instructor in Medicine at Ohio State University College of Medicine and was later Visiting Physician at White Cross, Mount Carmel and Grant Hospitals.

In 1931 he became Senior Attending Physician at Grant Hospital and in 1932, Senior Attending Physician at Mount Carmel Hospital. In 1933 he became Consulting Physician at Children's Hospital and in 1934 was appointed Endocrinologist of the Student Health Service of Ohio State University.

He became an Associate of the College in 1924 by virtue of his membership in the American Congress on Internal Medicine. He was a member of the Columbus Academy of Medicine, the Ohio State Medical Association and the American Medical Association.

Dr. Ramsey was an earnest student and occupied an enviable position as an internist in the State of Ohio. His many grateful patients, as well as his brother practitioners, mourn his passing so early in such a useful life.

A. B. BROWER, M.D., F.A.C.P.,
Governor for Ohio

DR. WARREN C. BREIDENBACH

Dr. Warren C. Breidenbach, F.A.C.P., of Dayton, Ohio, died June 29, 1942. He was born in Piqua, Ohio, on January 27, 1894, a son of Conrad W. and Elizabeth C. Steller Breidenbach.

Dr. Breidenbach received his preliminary education in Piqua and Dayton, and attended the University of Michigan, receiving his B.A. degree in 1914. He was graduated from the University of Michigan Medical School in 1917.

He was an interne and later resident physician at the Miami Valley Hospital. He entered the general practice of medicine and gradually developed his specialty in tuberculosis. He became Superintendent of the Stillwater Tuberculosis Sanatorium in 1919. He was also a member of the staff of Miami Valley Hospital, Good Samaritan Hospital, and a consultant at the Ohio Soldiers' and Sailors' Home at Xenia.

Dr. Breidenbach was a member of the Montgomery County and Ohio State Medical Societies, of the Mississippi Valley Tuberculosis Conference, and a Fellow of the American Medical Association. He was also a Fellow of the American College of Physicians, a member of the Trudeau Society, a member of the American College of Chest Physicians, a Diplomate of the American Board of Internal Medicine, and an assistant Fellow of the College of Thoracic Surgery.

He was especially interested in planography and developed it successfully in his study of tuberculosis. He is survived by his wife, Mrs. Elaine R. Breidenbach; two sons, Warren C., Jr., and Frederick, and a daughter, Jane. Dr. Breidenbach was highly successful in his specialty of tuberculosis. He devoted much of his time to a study of the prevention and treatment of tuberculosis in the indigent and many of his patients, especially from this group, will mourn his passing.

A. B. Brower, M.D., F.A.C.P.,
Governor for Ohio

DR. FRANCIS BACON CAMP

Dr. Francis Bacon Camp, F.A.C.P., died in St. John's Hospital, Springfield, Mo., on August 11, 1942. This brought to a close a life crowded with hard work and a considerable measure of success. Dr. Camp was widely known as an internist, and was also prominent in the social life of Springfield.

Born on December 31, 1896, in the city in which he died, he received his collegiate education at Westminster College and his medical education at Emory University. He served his internship in the St. Louis City Hospital, and after two years of further training began his practice in Springfield in 1925. He soon rose to prominence locally and throughout southwestern Missouri. He was deeply interested in developing the library of St. John's Hospital, and his friends are creating a memorial fund in his honor to be used to develop the library.

He was elected a Fellow of the American College of Physicians in 1941, and certified as an Internist by the American Board of Internal Medicine in 1939.

Hard work, devotion to his patients in a personal way, no doubt con-

tributed to the development of heart disease which eventually closed his career. He is survived by his widow, Mrs. Mary Peake Camp, a son, Walter Camp, and a daughter, Sally Camp, a brother, Dr. George Camp, and a sister, Mrs. Louis Spalding.

To these, we join his many friends and old patients in extending sympathy.

RALPH A. KINSELLA, M.D., F.A.C.P.,
Governor for Missouri

DR. WILLIAM FORSYTH MILROY

Dr. William Forsyth Milroy, a Fellow of the College since 1920, died at his home in Los Angeles, California, after a brief illness, at the advanced age of 87.

Dr. Milroy was born December 28, 1855, at York, New York. He received his premedical training at the University of Rochester. Following this he spent one year at Johns Hopkins University, one year at the College of Physicians and Surgeons at Baltimore, and was awarded his medical degree at Columbia University College of Physicians and Surgeons in 1883. He served his internship at the New York City Hospital and the New York Maternity Hospital.

For many years he practised medicine at Omaha, Nebraska, where he was an indefatigable worker, becoming successively President of the Omaha-Douglas County Medical Society, the Nebraska State Medical Association, and the Medical Society of the Missouri Valley. He was also Vice-President of the American Therapeutic Society in 1923. For 49 years he was Professor of Clinical Medicine at the University of Nebraska College of Medicine, in which capacity he was a source of the highest inspiration to the men with whom he came in contact.

Dr. Milroy made several contributions to the annals of medical lore, one of which, entitled "An Undescribed Variety of Hereditary Oedema," earned for him the distinction of being the discoverer of a pathologic condition henceforth to be known among medical men as "Milroy's Disease."

ROY E. THOMAS, M.D., F.A.C.P.,
Governor for Southern California

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1. Ivy, A. C.: The Applied Physiology of Bile Secretion and Bile Salt Therapy, J.A.M.A. 117:1151 (Oct. 4) 1941.

2. Reimann, Hobart A.: Treatment in General Medicine, Phila., F. A. Davis Co. 2nd Ed. Vol. I 1941, p. 851.

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4. Doe, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006–2008.

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